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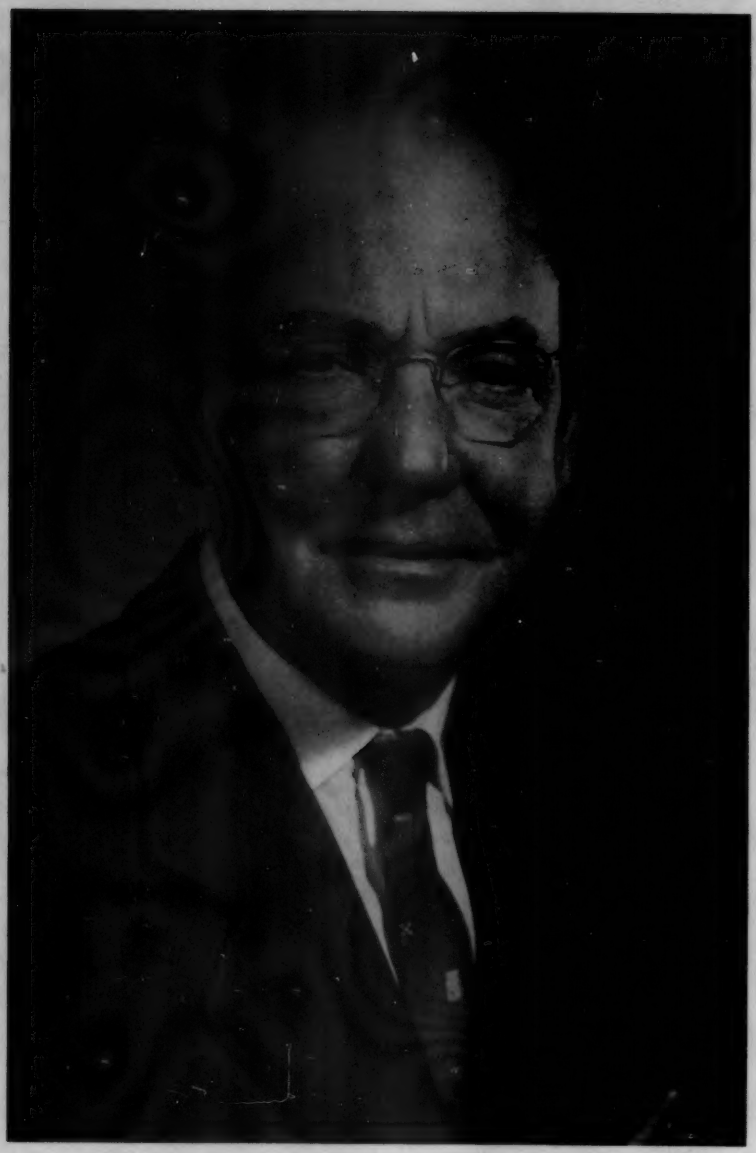

WILLIAM S. MacCOMB

Janeway Lecturer, 1960

THE AMERICAN JOURNAL OF ROENTGENOLOGY
RADIUM THERAPY AND NUCLEAR MEDICINE

VOL. 84 OCTOBER, 1960 No. 4

TREATMENT OF HEAD AND NECK CANCER*

JANEWAY LECTURE, 1960

By WILLIAM S. MACCOMB, M.D.
HOUSTON, TEXAS

CONTEMPORARY trends in medical thought normally have determined methods of treatment. In cancers of the head and neck, cautery, pastes and, occasionally, other surgical procedures were accepted forms of therapy until after 1858. That year, in his famous work, "Pathology of Tumors," Virchow established beyond doubt that cancer originated in the cell and that proliferation accounted for normal and atypical growth. It followed from this that malignant growth must be destroyed completely to effect permanent recovery. Ways and means of complete destruction were extended by the application of more scientific surgical procedures. Billroth's total laryngectomy and resection of the esophagus,[16] first performed on December 31, 1873, followed Virchow's explanation of tumor growth within fifteen years and led the way to general acceptance of more definitive surgery. By the turn of the century, radiation therapy was being used as an invaluable adjunct.

One of the leading figures in the transition from surgery to radiation therapy was Dr. Henry Harrington Janeway, an accomplished surgeon who intensively studied the physics of radiation to ensure a sound scientific basis for its use in cancer therapy. In 1912 he established the laboratory of radiation physics at the Memorial Hospital in New York and from then on, abandoning surgery, he devoted his energies and influence to the acceptance of radiation therapy as a treatment for patients with cancer. He obtained some of his best results in the treatment of patients with head and neck cancer. To be asked to deliver the Janeway Lecture is a great honor and I wish to express my appreciation to the Janeway Committee and the members of the American Radium Society for bestowing upon me this distinction.

Nearly fifty years have passed since Dr. Janeway turned his attention from surgery to radiation therapy, but, since he was both a surgeon and a radiation therapist, it seems particularly appropriate at this time to speak of the progress in the treatment of patients with head and neck cancer by surgery and by radiation therapy and by the combined use of both modalities.

* From the Head and Neck Service, University of Texas M. D. Anderson Hospital and Tumor Institute, Houston, Texas. Presented at the Forty-second Annual Meeting of the American Radium Society, San Juan, Puerto Rico, March 17–19, 1960.

HISTORICAL REVIEW

A century ago pessimism ruled surgical thought. In 1875 Sir John Erichsen declared in a public address that operative surgery had reached its furthest possible limits of development.[15] Sir Morell Mackenzie, a British laryngologist, stated in 1880 that "the only possible termination of cancer is death."[26] His assistant, J. Nolan Mackenzie, had written in 1879 that "there was never a thought of cure." Sir Morell Mackenzie was famous for having opposed a laryngectomy in the case of Crown Prince Frederick of Germany, in 1887.[18] Death would undoubtedly have resulted in this pre-Lister era. With conservative measures the Crown Prince survived long enough to ascend the throne on the death of his father. Frederick's rule lasted only ninety-nine days and he was succeeded by William II, the Kaiser who precipitated World War I. Only forty-three years earlier Ehrmann had made the first surgical effort to cure cancer of the larynx[16] but not until 1876 was a single cure reported.

In 1884 ex-President U. S. Grant was found to be suffering from cancer of the tonsil.[25] Metastatic cervical lymph nodes were present. A surgical procedure was considered but would have required splitting the mandible in the midline with complete extirpation of the tongue, tonsil and a part of the soft palate, together with the involved lymph nodes of the neck. The extent of the procedure, with the probability of involvement of tissues in proximity of major arteries and veins, and the lack of a guarantee that the borders of the disease could be reached, forced the surgeons, "in the best interest of the distinguished patient," to decline to recommend the procedure. The operation, although too extensive for that time, would be considered entirely feasible today.

Sir Henry T. Butlin, surgeon to St. Bartholomew's Hospital in London and an outstanding surgeon at the end of the nineteeth century, published a monograph in 1883 entitled "Malignant Disease of the Larynx." His conclusions were that "intrinsic cancer could not be removed by thyrotomy and that extrinsic cancer was a dire disease." In 1885 his monograph, "Diseases of the Tongue," was published; a second edition appeared in 1900.[5] The portion devoted to cancer is extremely interesting. In spite of numerous fatalities and what would have seemed to many of us to have been insurmountable odds, Butlin continued with his operative attempts at control of cancer of the tongue. He even extended the operation into the neck in the manner proposed by Kocher,[13] who excised a portion of the mandible and included the submental and submaxillary areas and the lymph nodes of the jugular chain. Butlin, however, did not enter the posterior triangle of the neck nor did he disturb the jugular vein.

In 1909, Butlin[6] presented a paper before the Royal Medical Society in London entitled "On the Early Diagnosis of Cancer of the Tongue and on Results of Operation in Such Cases." He reported that he had collected 100 cases of cancer of the tongue over a period of twenty-five to thirty years, that Whitehead of England had treated about the same number, Kocher of Switzerland had seen 100 to 120, and Billroth of Vienna had reviewed comparatively few. Butlin found in the British General Registry Office that, in the years 1901 to 1907 inclusive, 5,253 people had died of cancer of the tongue in England, an average of 750 per year. He estimated that of this number only 50 to 70 were treated successfully each year. He added that in America cancer of the tongue was regarded with absolute pessimism. One distinguished American surgeon had reported to Butlin that, in 36 patients operated for cancer of the tongue, there were only 2 known cures. Furthermore, an Austrian surgeon stated he knew of no cures at all. At the conclusion of his paper, Butlin stated he had recently seen a case of cancer of the tongue treated by the use of radium—unsuccessfully, however. He had also recently seen a patient with cancer of the buccal mucosa who had

been treated by the application of radium; there was such marked regression and improvement that Butlin foresaw this modality as a treatment for patients with tongue cancer as well. However, he recognized that even the smallest, earliest and most insignificant epithelioma of the tongue could produce cervical lymph node metastases and, therefore, he concluded that the surgeon would still be needed for the treatment of the regional metastases.

In 1906, in America, Dr. George Crile[8] presented a paper, "Excision of Cancer of the Head and Neck," before the Section on Surgery and Anatomy of the American Medical Association. His opening remarks were as follows: "Though signal advances have been made recently in many surgical problems, the treatment of cancer of the head and neck has, it would seem, neither received the attention nor kept the pace of progress in other fields. . . . The operative treatment is hampered by tradition and conventionality, and the tragic ending of so large a proportion of these cases has held back lay and even professional confidence." Crile had found that, in 4,500 cases of cancer of the head and neck coming to autopsy, death had resulted from the uncontrolled primary lesion or from regional metastases and that less than 1 per cent had died from metastases to distant organs or tissues. Therefore, he had become convinced of the necessity of performing a radical block dissection of the lymphatics of the neck. Crile described 1 instance in which he did a second radical neck dissection on a patient several months following the first procedure, removing the second jugular vein with no impairment of the circulation. In his series, although small, he proved that the patient with cancer of the head or neck who had a radical block dissection of the neck, in addition to excision of the primary lesion, had a 25 per cent better chance of living for three years without disease than one treated surgically for the primary lesion only. Though Crile's contribution was indeed epochal, many surgeons were slow in recognizing its importance and adopting the procedure.

The discoveries of Wilhelm Conrad Röntgen in 1895 and of the Curies in 1898, and the development and early application of the roentgen ray and radium in the treatment of cancer patients are too well-known to be repeated here. Enthusiasm in the use of these new tools for therapy of cancer patients soon moderated following realization of the dangers of over-treatment. Years of research and experimentation on the physical aspects of radiation were necessary before correct therapeutic levels could be ascertained. At Memorial Hospital, Failla and Quimby contributed solutions to many of these problems. Acceptance of radiation therapy was gradual in Europe and somewhat slower in the United States. The early work of Dr. Janeway and his associates, with its attendant difficulties and frequent discouragements, but with an increasing number of successes, is well-known to the members of the American Radium Society.

In 1922, in a "Symposium on Carcinoma of the Jaws, Tongue, Cheek and Lips" presented before the Clinical Congress of the American College of Surgeons in Boston, Crile[9] again emphasized the importance of treatment of the regional lymph nodes as well as of the primary cancer of the head and neck, as demonstrated by his results from the radical block dissection of the neck. At this symposium, Brewer[3] of New York presented statistics for the period 1900 to 1910 from the Roosevelt, Presbyterian and General Memorial hospitals in New York. The results were extremely poor but his conclusions are interesting. "From the statistics of this report which I believe to be accurate, it will be seen that the results of surgical treatment of the lip are far superior to those as yet obtained by radium, and that we are not justified at the present time in advising radium treatment in early operable cases. On the other hand, in cancer of the cheek, the results by radium are so evidently in advance of those obtained by operation, that until it can be demonstrated by a series of well observed three or five year cures, that operation

gives equally good results, all cancers arising in the mucous membrane of the cheek should be treated by radium."

At the same symposium, Judd and New[12] from the Mayo Clinic presented statistics showing gradual improvement in results over the years by using surgery in selected cases, reserving radium for inoperable cases only.

In the discussion of this symposium, Quick[24] defended the merit of radium in the treatment of cancer of the intraoral cavity and explained its technique in those early years, the external application using plaques and the interstitial application using radon emanation from glass tubes. Dr. Quick at that time was opposed to the radical block dissection of the neck, preferring to expose the lymph node and implant it with radon seeds. The statistics Dr. Quick presented were for a short term only but were suggestive of the better results to follow.

Through the ensuing years radiation therapy in the treatment of head and neck cancer gradually came into greater prominence and in some cancer centers superseded surgery. In the early years, radium, in the form of plaques and moulds, was used externally in the treatment of patients with cancer. In 1920 it was used experimentally in the form of needles, first externally and then interstitially, at the Curie Foundation and, at about the same time, in Brussels by Murdoch, Simon, and Stahel,[19] although their results were not reported until later. In Great Britain, early interstitial therapy of tongue cancer was reported by Evans and Cade.[10] In 1916 Failla, at Memorial Hospital, developed the radon glass tubes which he replaced with gold seeds in 1926. With the advent of the 200 kv. roentgen-ray machine in the early twenties, the therapeutic use of external radium gradually declined. Coutard's[7] technique of administering a prescribed dose of radiation over a period of approximately three weeks became universally accepted at that time, replacing the single dose technique. This method was particularly useful in the head and neck sites and gave an added impetus to the use of radiation therapy in the treatment of patients with squamous cell cancer.

At Memorial Hospital in the early thirties, the interest and endeavors of Dr. Hayes Martin,[17,18] Chief of the Head and Neck Department, were directed toward improving the end results in cases of head and neck cancer by the use of radiation therapy. For the most part this consisted of roentgen rays (200–250 kv.) administered in the manner proposed by Coutard to the primary lesion, supplemented with interstitial radiation in the form of gold filtered radon seeds if regression by external irradiation was incomplete. The cervical lymph nodes, if they were within the field of radiation to the primary lesion, were also treated by supplementary gold radon seed implantation when necessary. If they lay outside the field of the primary treatment, additional combined external and interstitial irradiation, or interstitial irradiation alone, was used. Persistent disease in the neck after radiation therapy was treated by a partial or radical neck dissection. These procedures were done under local anesthesia, block and infiltrative. Such operations for residual, irradiated, often ulcerated tumor were necessarily difficult and exhausting, both for the patient and the surgeon.

The statistical end results for cancer at various sites in the head and neck treated by radiation therapy at Memorial Hospital, as compiled by Martin over those years, showed increasing improvement. Discouraging effects from over-irradiation, seen in the earlier years, were noted less frequently. Sometimes late necrosis did occur, however, and was, no doubt, due to unequal distribution of the interstitial radiation. Occasionally, a new tumor was found growing in the area of previous irradiation. Pathologists gradually came to recognize these new tumors as sarcomas caused by radiation. The advanced stage of the disease, on first examination, often precluded all possibility of complete control by irradiation, although efforts of the lay press were gradually yield-

ing some results in bringing patients to their physicians for earlier diagnosis. All these facts caused the physician to turn again to surgical procedures for solution of some of these problems, particularly for the cancers in early or advanced stages.

Meanwhile, by trial and error, it had become apparent that squamous cell cancers presented varying degrees of radiosensitivity, some being almost radioresistant. Both radioresistant and radiosensitive types were found in the head and neck. Thyroid cancer soon was found to be radioresistant and radiation therapy for it was abandoned. Cancer of the intrinsic larynx had always been a surgical problem in the specialty of otorhinolaryngology; however, by 1940, patients with this lesion were being treated by partial or total laryngectomy performed by general surgeons interested in cancer. In the extrinsic larynx and hypopharynx, many cancers tended to show incomplete regression and renewed activity after treatment by irradiation, unless they had been treated in an early stage. Early involvement of cervical lymph nodes was the rule and control of regional metastases by external or interstitial irradiation was rare.

During the years of World War II, improvements in anesthesia, chiefly intratracheal intubation and the use of intravenous sodium pentothal, with freer use of blood transfusions, opened a new era in surgery. Later, the discovery of sulfanilamide and the release of antibiotics for civilian use decreased the likelihood of postoperative infection. Such procedures as the two stage laryngectomy of New[20] or the stage D operation of Portmann[23] leaving a pharyngostomy following a total laryngectomy were no longer necessary. Gradually the limits of the operative fields were widened. Cancer of the extrinsic larynx, which had yielded but poor or indifferent results with the use of radiation therapy, again could be treated by total laryngectomy.

Combining the operative procedures for tumors of the mouth, pharynx and larynx with those for their regional metastases became increasingly popular. Such procedures were not new; however, in earlier years they had been abandoned because of the exceedingly high mortality rate. With new developments in the surgical field these operative procedures became entirely feasible and offered distinct possibilities in improving end results. These combined operations, as described by Martin,[17] came to be known as the "commando" procedure or operation, a term particularly apt since the dictionary defines the word "commando" as a combined land and sea operation, first used in the Boer War.

The surgical field in head and neck cancer was extended rapidly in the post-war period of the forties. The over-all end results for any one anatomic site were undoubtedly improved but, too frequently, the disability of the patient resulting from such extensive sacrifice of tissue was deemphasized. The fact that the patient was alive at the end of five years and free of cancer was, as it should be, the main objective. But, in evaluating the end results for a particular anatomic site, three factors should be considered in this order, namely, (1) the curative results, (2) the functional result, and (3) the cosmetic result. These factors must be weighed in deciding upon the mode of treatment to be instituted for any patient.

Meanwhile, the radiation therapists had been perfecting their techniques. In 1934 Paterson and Parker[21] published a dosage system for gamma-ray therapy as applied to single plane implantation of superficial tumors. These authors later extended their system to include treatment of deep-seated tumors by means of volume implantation with low intensity radium needles. Their tables on dosage published in 1938[22] are now considered essential by all cancer therapists.

Of equal importance to the Paterson and Parker dosage tables in radium therapy was the report of Baclesse[1] in 1949 on his results obtained by extending the total treatment time of fractionated external

roentgen-ray therapy from the three weeks advocated by Coutard to six, eight or ten weeks. Baclesse, by extending the total treatment time, sought to avoid acute edema and severe reactions of the mucous membranes and still obtain complete regression of the disease. The works of Paterson and Parker and of Baclesse, with that of Coutard, remain the most outstanding contributions to radiation therapy in the second quarter of the present century.

Continued efforts were being made for improvement and it was not long before supervoltage was added to the armamentarium of the radiation therapist. In its early years, this type of therapy was not popular in treating lesions of the head and neck. The early supervoltage machines were more cumbersome and more difficult to manipulate than were the 200–250 kv. machines. As always occurs when initiating new methods or implements, the effects of which are somewhat uncertain, only advanced cases of cancer were selected for treatment by this type of therapy. Consequently, experience in supervoltage therapy for head and neck cancer was slow in accumulating and improved results were late in being demonstrated. Encouraging reports were published by some workers, however, such as those by Buschke, Cantril and Parker[4] in 1950. They were able to improve their results by using one field only, thus sparing a greater volume of tissue and overlying skin from the effects of radiation. These authors emphasized the importance of knowing the exact site of origin of a tumor rather than the amount of anatomic involvement, stating that the roentgen therapist could thereby evaluate the situation more precisely. They cited as examples such lesions as those of the aryepiglottic fold which, though bulky, respond well to irradiation, while those arising in the pyriform sinus and involving the aryepiglottic fold secondarily have a very poor prognosis with radiation therapy.

After 1945 the emphasis in regard to cancer therapy had swung again toward surgery and interest in radiation in some institutions waned. In only a few centers was an effort made to combine surgical treatment and radiation therapy. The report of Leroux-Robert[14] in 1950 from the Curie Foundation demonstrated the results of such a program begun in 1945. Four hundred patients with cancer of the extrinsic larynx were treated by total laryngectomy and postoperative radiation therapy. One hundred and fourteen survived for a minimum of three years—87 were supraglottic (30 per cent—three years) and 27 were in the pyriform sinus (22 per cent—three years). In the following year, an excellent report was published on combined therapy in intraoral cancer by Wookey, Ash, Welsh and Mustard[27] from Toronto. It was evident then that in some centers the need for a joint effort was recognized as essential in the treatment of head and neck cancer.

At the University of Texas M. D. Anderson Hospital, where it has been my good fortune and pleasure to be associated with Dr. Gilbert Fletcher and his department of radiation therapy for the past eight years, patients with head and neck cancer are treated by radiation therapy or surgery, or both. The modality is chosen according to the site and extent of the disease at the time of the patient's admission to the Head and Neck Clinic. In general, patients with lymphomas are treated by irradiation, those with salivary gland tumors and tumors of the thyroid are treated surgically. Sarcomas, aside from lymphosarcoma, are comparatively rare in the head and neck region and, except for lymphosarcomas, are a surgical problem. Squamous cell cancers at this institution make up the largest percentage of malignant tumors and frequently both surgery and radiation therapy are needed.

PATIENTS PREVIOUSLY TREATED

Since the M. D. Anderson Hospital is a state hospital, many patients arrive with the disease in an advanced stage; however, few are turned away as untreatable. Many have been previously treated by irradiation or by surgery, usually inade-

quately. Previous radiation therapy precludes its use for further treatment, since a full tumor dose of radiation cannot be applied to tissues previously treated in this manner. If the therapy administered before admission has not been excessive or if the disease is not too advanced, the patient is accepted. For 143 patients treated prior to admission to M. D. Anderson Hospital during the past eight years, the anatomic distribution of the primary site of the cancer and the end results are shown in Table 1. In some instances, previous treatment may not have detracted from the ultimate control of the disease but usually the first treatment, whether by irradiation or by surgical resection, should be radical enough to ensure a reasonable chance of controlling the tumor. Certainly, the first treatment is the most important and gives the best hope of cure.

Patients with no treatment prior to admission to the M. D. Anderson Hospital are admitted for (1) radiation therapy, (2) surgery, or (3) both.

TABLE I

SURVIVAL RATE OF PATIENTS TREATED BEFORE ADMISSION TO M. D. ANDERSON HOSPITAL

Site	No. of Cases	Survival after Treatment (yr.)	Survival Rate*	Standard Error†
Oral Cavity	87	1	73.3	4.7
		2	56.4	5.5
		3	*48.0*	*5.8*
		4	45.7	6.0
		5	*35.9*	*6.8*
Oropharynx‡	14	1	55.6	13.5
		2	31.8	12.9
		3	*31.8*	*12.9*
		4	22.7	12.0
		5	*22.7*	*12.0*
Extrinsic Larynx (supraglottic and pyriform sinus)	23	1	78.3	7.8
		2	53.8	10.8
		3	*46.6*	*11.5*
		4	46.6	11.5
		5	*25.9*	*12.7*
Intrinsic Larynx	19	1	89.2	7.2
		2	89.2	7.2
		3	*89.2*	*7.2*
		4	89.2	7.2
		5	*73.0*	*11.4*

* Cumulative survival rate according to Berkson and Gage.[2] Three and five year results are italicized.

† Standard error according to Greenwood.[11]

‡ Oropharynx includes the palatine arch (soft palate, anterior tonsillar pillar and retromolar trigone) and pharynx (faucial tonsil, base of tongue and pharyngeal wall).

TUMORS PRIMARILY TREATED BY RADIATION THERAPY ONLY

Radiation therapy is the treatment of choice for most intraoral squamous cell cancers. Primary cancer of the tongue responds particularly well to interstitial radium therapy in the form of volume implantation with needles of low intensity. Recurrences or complications of necrosis are rare but, when they do occur, they are managed by surgical resection. External irradiation alone, or combined with interstitial therapy similar to that used for the tongue, is the treatment of choice for patients with lesions of the buccal mucosa. For the floor of the mouth, volume implants alone are preferred.

Radiation therapy remains the only accepted treatment for cancer of the nasopharynx and is accomplished satisfactorily by external irradiation only, using the Baclesse method. Cancers of the oropharynx include lesions of the palatine arch (soft palate, anterior tonsillar pillar, retromolar trigone) and the pharynx (base of the tongue, faucial tonsil and wall of the pharynx). Squamous cell carcinomas arising in these primary sites are rather markedly radiosensitive and all are treated by radiation therapy. An excellent response with complete subsidence of disease is to be expected. Supervoltage radiation, using either cobalt 60 teletherapy or the betatron, is the modality of choice, since skin reactions are less than with orthovoltage therapy. Many patients with cancer of the oropharynx, particularly of the soft palate and base of the tongue, present with cervical lymph node metastases. Since the subdigastric region is the area in the neck where regional metastases most fre-

quently appear first, the metastatic areas are usually included in the treatment field of the primary lesion. Should regression of the primary lesion be incomplete or should reactivity occur in either the primary or the secondary site, or both, surgery is performed after radiation therapy.

Cancer of the hypopharynx occurs most frequently in the lateral pharyngeal wall or the pyriform sinus. The difficulty in classifying lesions of the pyriform sinus is apparent. If the cancer definitely arises on the medial wall of the fossa, it should be classified as extrinsic larynx, since the site of origin is a part of the larynx proper, but if it is on the lateral wall, then it is part of the hypopharynx. Most lesions of the pyriform sinus are so advanced that it is impossible to determine the exact site of origin. Some authors prefer to classify this group as a part of, but separate from, the extrinsic larynx proper. The same problems of classification apply to the postcricoid region for similar reasons.

Primarily, radiation therapy is used for cancer of the lateral and posterior walls of the hypopharynx.

Cancer of the pyriform sinus is usually not seen in its early phase. Cervical metastases are often already present. The rare early exophytic lesion of the pyriform sinus responds well to radiation therapy. Occasionally, a more advanced lesion may be treated by irradiation if, for medical reasons, surgery is contraindicated.

Early cancer of the intrinsic larynx, the true vocal cord, should be treated by external radiation therapy using the Baclesse technique. At no time does the patient suffer any real discomfort from this type of treatment. A month to six weeks after completion of therapy the reaction will have subsided with complete regression of the disease and recovery of a normal speaking voice. Even in those patients who have cancer of the true vocal cord, which presents in a moderately advanced stage, radiation therapy is justified. Those lesions are termed "moderately advanced" which are not confined to one true cord but have progressed across the anterior commissure to the opposite cord or are infiltrating beyond the confines or the cord proper, as shown by beginning paralysis of the vocal cord.

Early cancers of the supraglottic region (extrinsic larynx) of the exophytic type are treated by radiation therapy. Lesions of the epiglottis, however, because of the early invasion of cartilage by the cancer, do not respond as well to radiation therapy as do those at other sites in the extrinsic larynx. Even if the attempted treatment by irradiation should fail, a total laryngectomy may still be done without fear of increasing the morbidity for the procedure.

TUMORS PRIMARILY TREATED BY SURGERY ONLY

Cancers of the skin and lip are prevalent in the southwestern region of the United States due to exposure to sun, wind and dust. The preferred treatment for patients with these lesions is surgical resection. Many lesions are multiple and many also are extensive, often involving the entire external nose or ear. The largest number are basal cell in character but, when these lesions invade cartilage or bone, they are as destructive as the squamous cell cancers. The latter may produce preauricular and cervical lymph node metastases, for which a radical neck dissection and parotidectomy are indicated. For those patients who are returning to their former occupations in the same climatic conditions, surgery seems preferable to radiation therapy. The latter treatment is sometimes selected for the more aged person who will no longer be subjected to overexposure to sun. The surgical procedure may consist of local excision for small lesions. For more extensive lesions, a greater sacrifice of tissue is required with repair by skin grafts. For cancer of the lip, a V-excision with immediate closure or repair by Estlander or Bernard triangles is effected with very satisfactory results. The frozen section examination by the pathologist of the borders and base of the specimen at the time of excision is essential.

Only early lesions of the oral cavity

(tongue, floor of the mouth or buccal mucosa) are selected for surgical excision. Hard palate and upper gum lesions are entirely a surgical problem, the extent of the resection depending upon the amount of involvement. Repair of resulting surgical defects of the upper jaw is accomplished by means of a dental prosthesis.

Surgical extirpation is the selected treatment for most lesions of the supraglottic region of the extrinsic larynx. Treatment is limited to resection only when the pathologist has reported a satisfactorily wide margin free of disease on all borders of the surgical specimen.

In cancer of the cervical esophagus, only surgical excision is used when the disease is limited and the pathologist reports that all borders and the base of the surgical specimen are clear.

TUMORS PRIMARILY TREATED BY COMBINED THERAPY

In the treatment of head and neck cancer, the use of both irradiation and surgical treatment is often necessary in order to control the disease. Combined therapy may be planned because of the site or extent of the tumor when the patient is first examined. It may also be unplanned. In cases where there is recurrence of the tumor following the use of one modality, the other is utilized in the treatment of the recurrence.

PLANNED COMBINED THERAPY

Butlin[6] stated fifty years ago that radium might become effective in the treatment of intraoral cancer; however, he felt that surgery would still be needed in the treatment of regional metastases. Such has proved to be the case and both radiation therapy and surgery are necessary in treating the many patients with cancer of the head and neck regions. Patients who have cervical lymph node metastases from intraoral cancer are best treated by radical neck dissection following completion of radiation therapy to the primary lesion. Approximately four weeks should elapse before the neck dissection is carried out. Preoperative irradiation of palpable regional metastases, most often in the subdigastric region, is frequently used on the Head and Neck Service of M. D. Anderson Hospital. A tumor dose of 4,000 to 4,500 r is administered through a small field to the area of the metastases in the cervical lymph nodes over a period of five to seven days while the primary lesion is being irradiated. Such irradiation restrains the growth of the neck metastases until the radical neck dissection can be performed four to six weeks after completion of treatment to the primary tumor. Irradiation of the primary lesions of oropharynx or hypopharynx usually includes areas of cervical lymph node metastases. Surgical dissection of the neck is employed only in cases where there is incomplete regression of the metastatic lymph nodes. The use of a partial neck dissection should be abandoned. If the neck is to be entered surgically, the entire procedure should be accomplished at one time. The possibility of metastases occurring in a portion left undissected is too great to permit a lesser procedure initially. Poor general condition of the patient is sometimes advanced as the reason for the performance of a partial neck dissection; however, the additional time needed for completing a radical procedure is comparatively slight.

The classic neck dissection, as has been frequently defined, extends from the inferior line of the mandible above to the clavicle below, and from the midline of the neck anteriorly to the anterior border of the trapezius posteriorly, removing the sternocleidomastoid muscle, the internal jugular vein and all lymph node bearing areas. The sacrifice of the spinal accessory nerve was early considered advisable. In the absence of metastatic lymph nodes, clinically undemonstrable at the time of the operation in such instances as the commando operation, where the neck dissection is done regardless of the presence of cervical lymph node involvement, the spinal accessory nerve may be preserved. In all other instances the nerve should be sacrificed. Oc-

casionally, an end to end anastomosis may be accomplished. In other cases the great auricular nerve, ordinarily sacrificed during the operative procedure, may be used as a graft to repair the spinal accessory.

The hypoglossal and vagus nerves with the cervical sympathetic chain may also be excised when involved with metastatic disease, without hazard to the patient. In fact, the confines of the radical neck dissection have now been broadened to encompass the removal of all structures on one side of the neck even to and including the common and internal carotid with replacement of these vessels by a nylon prosthesis. A radical neck dissection is not indicated except in cases of proved metastatic cancer and as a part of the commando procedure.

Bilateral neck dissections are frequently carried out without any particular hazard to the patient. In the past eight years this procedure has been performed on over 70 patients on the Head and Neck Service at M. D. Anderson Hospital without mortality and without disability, even in patients from seventy to eighty years of age.

An example of the need of a bilateral neck dissection for an intraoral primary lesion is shown in the following case report:

G.A. This forty-two year old female was admitted on January 19, 1959 with a two month history of an ulcer in the floor of the mouth. Examination showed the lesion to be 3 cm. in diameter. The 8 remaining teeth in the lower jaw were in poor condition. A lymph node in the left subdigastric and one in the right preglandular region were found to be clinically positive. Biopsy of the primary tumor revealed squamous cell carcinoma, Grade II–III. A roentgenogram showed the mandible to be essentially negative. Treatment began on January 21, 1959 with the extraction of all remaining teeth. On January 29, 1959 a radium implanation was carried out, delivering a tumor dose of 8,000 r. Good reaction and regression resulted. A left radical neck dissection was performed on February 25, 1959. Microscopic examination showed 3 lymph nodes to be positive. On March 25, 1959 a right radical neck dissection was carried out and microscopic examination revealed 1 positive lymph node. The patient has remained free of disease for one and a half years (Fig. 1, *A* and *B*).

The need of performing a tracheostomy in major operative procedures in the head and neck area is now becoming increasingly well recognized. For the House Staff of the M. D. Anderson Hospital, the following indications for performing tracheostomy have

Fig. 1.—(*A* and *B*) Photographs showing minimal amount of scarring and edema from bilateral radical neck dissection.

been made: (1) when performing a commando procedure; (2) when performing the second of a bilateral neck dissection; (3) when performing a partial resection of the mandible; (4) if a tracheostomy has been performed at any previous time; (5) if radiation therapy has been given to the larynx (irradiated tissues of a larynx become edematous following the use of intratracheal tubes for anesthesia); and (6) in many aged debilitated persons tracheostomy has been found of great aid in the postoperative care since suction of the respiratory tract can then be carried out effectively, preventing pulmonary complications.

Many patients with advanced intraoral lesions are treated at the M. D. Anderson Hospital. Were the surgical procedure alone to be used for complete extirpation of the primary lesion, the amount of intraoral tissue to be removed would be so great that primary closure would be difficult and the functional result for the patient would be unsatisfactory. By using radiation therapy before surgery, at times delivering slightly less than a full tumor dose, the amount of tissue to be excised from the primary site is decidedly less than would have been necessary with surgery alone. Increased morbidity following preoperative irradiation and surgery is recognized, but this fact is more than offset by the improved prognosis and the better functional result obtained for the patient. Delay in healing sometimes does occur. If the radiation given through the operative field is not over 6,000 r tumor dose, little difficulty in healing will be encountered. Fatalities have occurred from necrosis of the common and internal carotid arteries. Removal of the artery and replacement with a prosthesis have proved not to be feasible in an irradiated field. Fortunately, mortality from this complication is rare and with better experience and judgment should be avoided. The concensus at M. D. Anderson Hospital is that supervoltage therapy causes fewer complications than orthovoltage therapy.

UNPLANNED COMBINED THERAPY

For the recurrent cancer of the intraoral cavity managed originally by radiation therapy, surgical procedures are used. Further irradiation would, of course, be hazardous, the likelihood of necrosis being great. For the same reason second intraoral primary lesions are treated by excision if the first lesion was irradiated. The extent of the surgical procedure depends on the site of the tumor and amount of the involvement.

For the occasional necrosis resulting from the radiation treatment of the primary intraoral lesion, operative procedures are sometimes necessary. Necrosis most frequently occurs after irradiation of the floor of the mouth because of the proximity of the radium needles to the mandible. In most instances, the area of necrosis is relatively small and will respond to the use of topical applications of zinc peroxide paste. Exposure of bone is best treated conservatively, permitting fragments of necrotic bone to sequestrate spontaneously if possible. Rarely is necrosis so extensive as to require alcohol injection for relief of pain. Should partial resection of the mandible be necessary, it is done by the intraoral route. Healing is uncomplicated and the end result satisfactory. An example of the unplanned use of radiation therapy and surgery in treatment of cancer of the floor of the mouth is shown in the following case report:

J.M. This fifty year old male was admitted on February 15, 1954 with a history of a sore in the floor of the mouth for one year. On examination, the patient presented a lesion to the left of the frenum measuring 3×1.5 cm. in size (Fig. 2*A*). No lymph nodes were palpable. The biopsy report was squamous cell carcinoma, Grade II. The roentgenographic examination showed no bone invasion of the mandible. Five lower teeth were extracted before a volume implantation, delivering 7,000 r tumor dose, was performed on February 26, 1954. A small area of possible recurrence, 1.5 cm. in diameter, was found on February 24, 1956. Biopsy showed squamous cell carcinoma, Grade II,

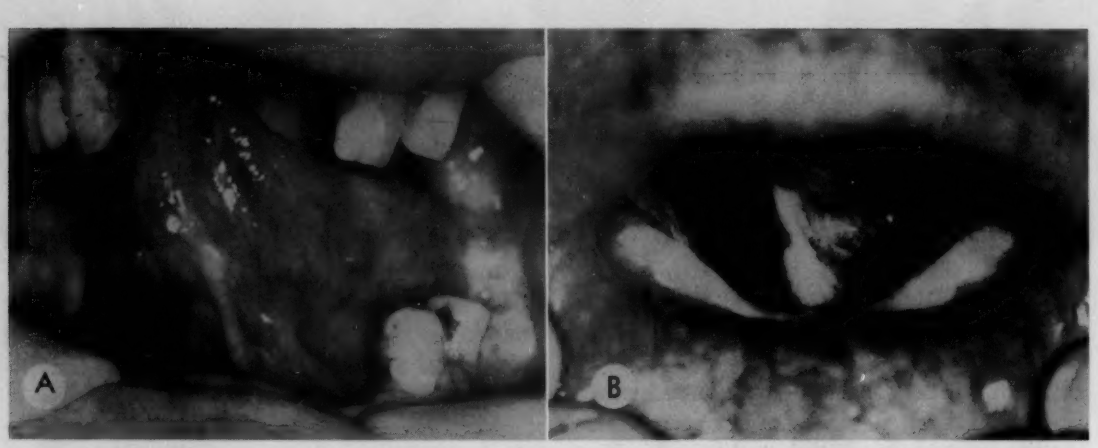

Fig. 2. Photographs of cancer of the floor of the mouth treated by radium implantation and later by excision and skin graft for area of recurrence. (*A*) Before treatment. (*B*) After treatment.

with limited invasion. On March 1, 1956 a surgical procedure consisting of a marginal resection of the mandible, local excision of the area of recurrence, and a skin graft to the floor of the mouth was carried out. The patient has remained free of disease four and one-half years (Fig. 2*B*).

Another example of unplanned combined therapy is shown in the following case report:

M.W. This forty-eight year old male was admitted on January 13, 1958 because of a persistent sore throat of one month's duration. The patient was found to have a lesion, 4 cm. in diameter, on the right side of the base of tongue and glossopharyngeal sulcus, invading the tonsil. The report from the pathology department was squamous cell carcinoma. From January 20 to February 21, 1958, by means of cobalt 60 teletherapy and 22 mev. betatron, over a period of thirty-three days and twenty-one treatment days a tumor dose of 6,050 r was administered. On February 25, 1958, under local anesthesia, 4,320 r was given in addition to the external radiation by means of radioactive gold grains (Au^{198}). A diagnosis of residual disease was made on December 17, 1958, when the induration in the right posterior border and base of the tongue, previously observed, was found to be more marked. On December 21, 1958 a right commando procedure was done. Squamous cell carcinoma infiltrating fibrous tissue and voluntary muscle was reported but no lymph nodes in the operative specimen were positive for metastatic cancer. Examination on April 8, 1959 revealed clinically renewed activity on the right side of the intraoral cavity. The biopsy was positive. A volume implantation with radium needles of low intensity delivering 5,600 r was carried out. Residual disease was again evident with a positive biopsy report on June 24, 1959. On July 17, 1959 a subtotal glossectomy was performed. The examination of the intraoral cavity on September 23, 1959 was negative but an enlarged left subdigastric lymph node was present. On September 25, 1959 a left radical neck dissection was performed with the pathologist reporting one subdigastric lymph node as positive. Figure 3, *A* and *B* are recent photographs of the patient. He remains free of disease.

For cancer of the oropharynx and hypopharynx, the combination of radiation therapy and surgery is not planned as frequently as in cancer of the intraoral cavity. This group of lesions is more radiosensitive in both the primary and secondary sites than are the intraoral lesions. Persistent or recurrent disease in any of these sites following the use of radiation therapy is treated by resection, the extent of the resection depending upon the site and extent of the primary lesion and upon the presence of proved regional lymph node metastases.

Persistent disease in the tonsil, retromolar trigone, or base of tongue is best treated by a commando procedure. Residual or recurrent disease in the posterior pharyngeal wall is best approached through an infrahyoid incision. Excision of the area

Fig. 3. (*A* and *B*) Photographs of patient treated for cancer of the tongue by radiation therapy and surgery.

of disease may be accomplished and primary repair of the wound carried out, or repair may be effected by the use of a split thickness skin graft. For large defects a pharyngastomy is performed and repair is completed later by means of a tube graft. Approach to recurrent or residual disease in the lateral pharynx is by lateral pharyngotomy combined with a radical neck dissection if proved metastatic lymph nodes are present. The need of both modalities is exemplified by the following case reports:

M.R. This sixty year old male was admitted on August 8, 1956 with a history of hoarseness for three months and hemoptysis of one month's duration. No difficulty in swallowing was experienced until a biopsy was taken by a physician in another city. The patient presented two lesions, one arising in the left false cord causing complete paralysis of the left side of the larynx, the second on the left posterior and lateral pharyngeal walls. Biopsies of both lesions showed squamous cell carcinoma, Grade III. Roentgenographic studies showed an extensive tumor of the hypopharynx, beginning at the upper border of the epiglottis and extending downward on the left side into the subglottic region (Fig. 4, *A* and *B*). A tumor dose of 7,200 r by means of cobalt 60 teletherapy was given from August 8 to September 21, 1956. Nine days after completion of therapy a laminagram of the larynx (Fig. 5) showed persistent edema. On June 24, 1957, clinical examination showed the larynx to be immobile with reactivity in the posterior pharyngeal wall. Roentgen studies (Fig. 6, *A* and *B*) at that time showed recurrent disease of the pharynx. On July 3, 1957 local excision of an area 1.5×2 cm. was performed through an infrahyoid approach. The pathologic report was squamous cell carcinoma, Grade III, with the borders and the base free. Primary closure was effected. The postoperative course was uncomplicated except for persistence of edema which eventually subsided. The patient is still free of disease, four years after admission and three years after the last evidence of activity.

M.P. This sixty-eight year old male was admitted on November 20, 1956 with persistent hoarseness which had been present for two months. A right subdigastric lymph node had been removed for biopsy. The pathologic report was squamous cell carcinoma. The patient received radiation therapy by means of the 22 mev. betatron from November 20, 1956 to January 4, 1957. A tumor dose of 6,900 r was delivered. In September, 1957, he presented an area of residual disease at the right side of the base of the tongue inferiorly, involving the vallecula and the lingual surface of the epiglottis. The report from the biopsy was squamous cell carcinoma. On October 1, 1957 a total

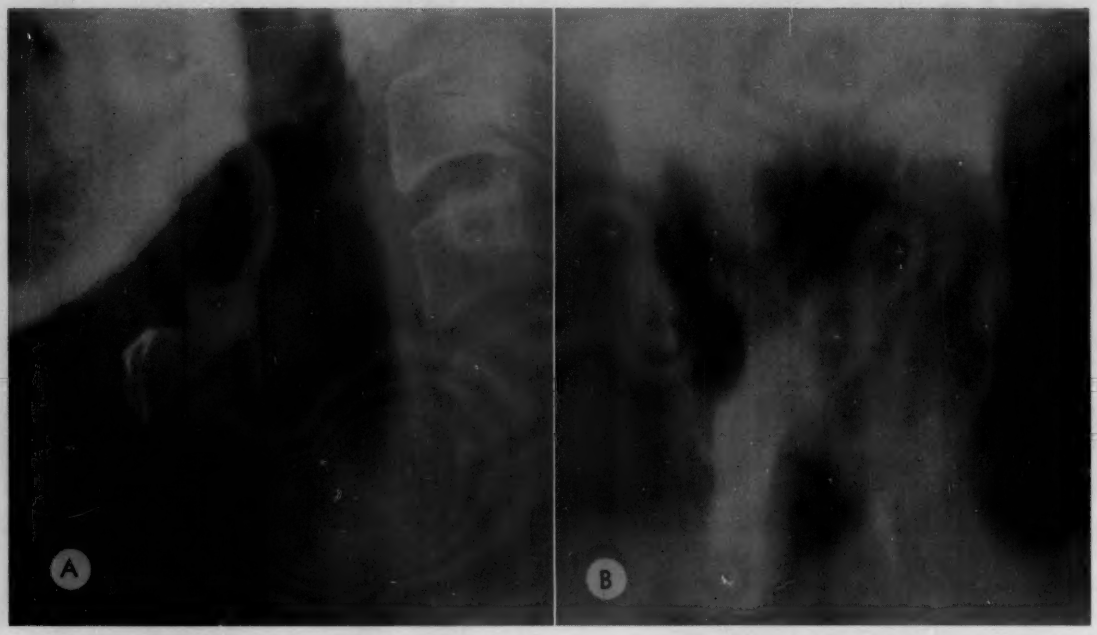

Fig. 4. (*A* and *B*) Roentgenographic studies showing the extent of the lesion of the hypopharynx (posterior and lateral pharyngeal walls) and the left false cord before treatment by radiation therapy.

laryngectomy with excision of the base of the tongue on the right side was performed, leaving a pharyngeal stoma for subsequent closure (Fig. 7*A*). Plastic repair was begun in January, 1958.

Fig. 5. Same patient as in Figure 4. Laminagram shows a decrease in the size of the primary tumor of the false cord with persistent edema following completion of radiation therapy.

A right radical neck dissection was performed on March 14, 1958 because of the presence of an enlarged prevascular lymph node. Microscopically, this was the only evidence of disease in the right side of the neck. Closure of the pharyngeal stoma was completed on January 26, 1959. Two and one-half years after total laryngectomy and one and one-half years since completion of the closure of the pharyngeal stoma, the patient is free of disease (Fig. 7*B*).

W.B. This sixty-five year old white male was admitted on February 17, 1954 with a complaint of soreness in the left lower gum which had been present for two months. Examination revealed a lesion, 2.5 cm. in diameter, in the region of the retromolar trigone, invading the tonsillar pillar and the base of the tongue. One subdigastric lymph node was palpable. The report on the biopsy was squamous cell carcinoma, Grade II. A modified pterygoid tongue implant with radium needles of low intensity delivering a tumor dose of 4,800 r was inserted on March 2, 1954. From March 8 to March 19, 1954, by external irradiation with the 250 kv. machine, an additional 2,000 r was delivered to a field 8×8 cm. The patient remained free of disease three and one-half years. On November 26, 1958 a biopsy revealed the presence of cancer in the left

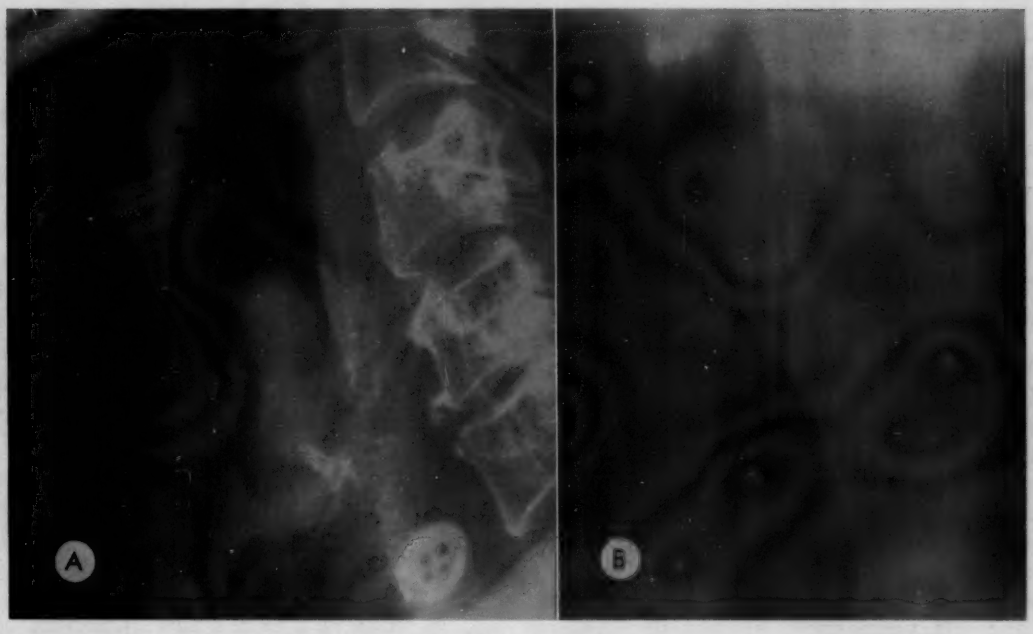

Fig. 6. (*A* and *B*) Roentgen studies show recurrent disease on the posterior lateral pharyngeal wall nine months after completion of radiation treatment.

vallecula and the base of the tongue. Bilateral lymph node involvement was also present. A total laryngectomy was performed on December 15, 1958 with the pathology report showing involvement of the base of the tongue, anterior surface of epiglottis, lateral surface of aryepiglottic fold, false cord and the left pyriform sinus. Aspiration biopsy of a left midjugular lymph node was also reported positive. Radiation therapy by means of cobalt 60 was given from January 6 to February 6, 1959. A tumor dose of 5,000 to 6,000 r was delivered to each

Fig. 7. Photographs of patient with extensive cancer of the base of the tongue treated by combined radiation therapy and surgery, showing pharyngeal stoma following total laryngectomy (*A*) and closure of stoma after tube graft (*B*).

side of the neck with an additional 1,500 r (skin dose) to the left side. The neck lymph nodes regressed and a proposed right radical neck dissection was not done. The patient has remained free of disease one and one-half years.

In the intrinsic larynx, combined irradiation and surgery is used in those instances in which recurrence takes place in a cancer of the true vocal cord previously treated by radiation therapy. An example is shown in the following case report:

O.S. This sixty-seven year old male was admitted on September 27, 1955 with a complaint of hoarseness for a period of six months. He stated that he had chewed tobacco and used snuff since the age of eight and had been smoking 2 packages of cigarettes daily since the age of twenty. Clinical examination revealed an exophytic lesion in the middle third of the left vocal cord, without decrease in mobility. The biopsy specimen showed squamous cell carcinoma, Grade II. Radiation therapy delivering a 5,400 r tumor dose by means of cobalt 60 was given from October 12 to November 15, 1955 in twenty treatment days. Six months later, on June 1, 1956, the examination was negative, the voice normal, and all edema had disappeared. Almost three years later, on February 18, 1959, the patient was referred back to this institution by his local otolaryngologist because of renewed activity of the lesion and a positive biopsy. No cervical lymph nodes were palpable. A total laryngectomy was done on March 11, 1959 and the patient has remained free of disease since that time, a period of one and one-half years since the laryngectomy and nearly five years since the initial treatment.

Both surgical resection and radiation therapy are required for management of cancer of the intrinsic larynx too advanced for expected control by radiation therapy alone. Postoperative radiation therapy is employed in those instances where the pathologist has reported from the whole organ studies of the larynx that the disease has extended outward through lymphatic channels beyond the margins of the cut surgical specimen. The tracheal stoma is included in the field of irradiation only in case of subglottic extension of the primary lesion. In cancer of the intrinsic larynx invading the anterior commissure, the presence of a positive Delphian node is not unlikely. In those patients, radiation therapy, in the form of a volume implantation of the pre-epiglottic space, is carried out with satisfactory results.

For the average lesions of the supraglottic region, the false cord, arytenoid, aryepiglottic fold and epiglottis, a total laryngectomy is done with a radical neck dissection, if proved metastatic lymph nodes are present; bilaterally, if necessary. A thyroid lobectomy on the affected side is advisable, as metastases to this area are not infrequent and recurrences have been noted in this organ when the thyroid lobe on the side of the primary lesion has been left in place. Routine postoperative radiation therapy is administered if regional metastases are present or if the report of the pathologist indicates the probability of further activity. The tracheal stoma is shielded from irradiation, since this tends to produce crusting of the upper limits of the trachea during the period of treatment, and excessive dryness and discomfort occur after healing from irradiation is complete. A case report of a patient with supraglottic cancer follows:

D.J. This white forty-eight year old male was admitted to M. D. Anderson Hospital on December 28, 1953 with a history of hoarseness of one year's duration. Eleven days before admission a lymph node on the left side of the neck had been removed by his physician and reported as squamous cell carcinoma, Grade II. Clinical examination revealed a lesion of the left false cord, arytenoid, aryepiglottic fold and pyriform fossa. The wound in the left cervical region was incompletely healed. A biopsy from the left false cord verified the report of squamous cell carcinoma, Grade II. When a total laryngectomy and left radical neck dissection were performed on January 1, 1954, it was found that the lesion of the larynx arose from the left aryepiglottic fold and false cord and invaded the pyriform fossa. With conventional therapy the cervical regions were irradiated postoperatively through lateral fields, two on either side. During an interval of forty-four

days, or thirty-two treatment days, a tumor dose of 6,000 r was administered to the midline of the neck and 4,500 r to the suprahyoid region. The pathologist reported no other metastatic lymph nodes in the neck but whole organ studies revealed disease near the anterior and left superior margins of the surgical specimen. For this reason, four days after completion of the external therapy (March 16, 1954), supplemental interstitial radiation was given in the pre-epiglottic spaces, using a volume implant of low intensity radium needles. An additional tumor dose of 6,300 r was delivered to the anterior hyoid region. For nearly two years the patient remained well and without complaints. On January 4, 1956, when he came to the clinic, he was found to have a draining sinus in the hyoid region from necrosis of the cartilage. On January 19, 1956 the hyoid was resected and healing resulted without complications. During the past six and one-half years the patient has remained free of disease. He has an excellent post-laryngectomy voice and carries on his normal business activities as a clerk.

Cancer of the pyriform sinus yields poor statistical end results by either radiation therapy or surgery. With both modalities combined a somewhat better cure rate is obtained. Many lesions of the pyriform sinus extend upward along the pharyngeal wall and undoubtedly are best classified as hypopharynx primaries. A total laryngectomy and a thyroid lobectomy with a radical neck dissection, in the presence of proved metastatic lymph nodes on the side of the primary lesion, are performed, followed by postoperative radiation therapy when surgical healing is complete. Skin grafts are used if the amount of remaining mucosa is insufficient for primary closure. The formation of a pharyngeal stoma with a secondary closure by a plastic procedure later may be advisable. Postoperative radiation therapy should be delayed until the fistula is completely closed since the administration of radiation on moist skin is inadvisable. In the presence of bilateral metastatic lymph nodes, a bilateral neck dissection is carried out with the total laryngectomy, followed by postoperative radiation therapy, though the prognosis is poor. Examples of pyriform sinus lesions with and without neck lymph node involvement are shown in the following case reports:

C.O. This fifty-six year old male was admitted on March 9, 1954 with complaints of a sore throat and difficulty in swallowing which had persisted for nine months. Clinical examination showed a lesion in the right lateral pyriform sinus extending upward along the pharyngeal wall. A mass palpable in the neck over the area of the primary lesion was thought to be direct extension. Biopsy showed squamous cell carcinoma, Grade III. A total laryngectomy and right radical neck dissection plus a partial pharyngectomy were done on March 23, 1954. Direct extension necessitated wide removal, with repair by skin graft and formation of a pharyngeal stoma. The pathologist reported squamous cell carcinoma, Grade III, of the pyriform sinus with direct extension through the thyroid cartilage and metastatic carcinoma in two jugular chain lymph nodes. Because a prolonged period was anticipated before closure of the pharyngeal stoma could be completed, radiation therapy was given from April 26 to June 1, 1954 by means of cobalt 60 teletherapy through right and left fields, 13×17.5 cm. and 9×7 cm. During the twenty-seven treatment days a tumor dose of 6,200 r was delivered (Fig. 8, *A* and *B*). Tube graft repair was performed in 6 stages and completed on July 27, 1956. The patient is well and free of disease six years after his admission (Fig. 9).

M.A. This fifty-three year old male was admitted on August 3, 1953 with a history of hoarseness, cough and shortness of breath of two and one-half months' duration. The patient presented with a large mass arising in the left pyriform sinus, extending upward along the left lateral wall of the pharynx, invading the left half of the larynx and obstructing the glottic space. There were no palpable lymph nodes in the neck. Report on the biopsy specimen was squamous cell carcinoma. Roentgen studies showed an extensive lesion of the left side of the larynx, involving the left pyriform sinus, left aryepiglottic fold, and upper lateral half of the epiglottis (Fig. 10, *A* and *B*). A total laryngectomy was performed on August 7, 1953 followed by radiation therapy. A tumor dose of 6,000 r was administered by means of the 250 kv. machine during the period from

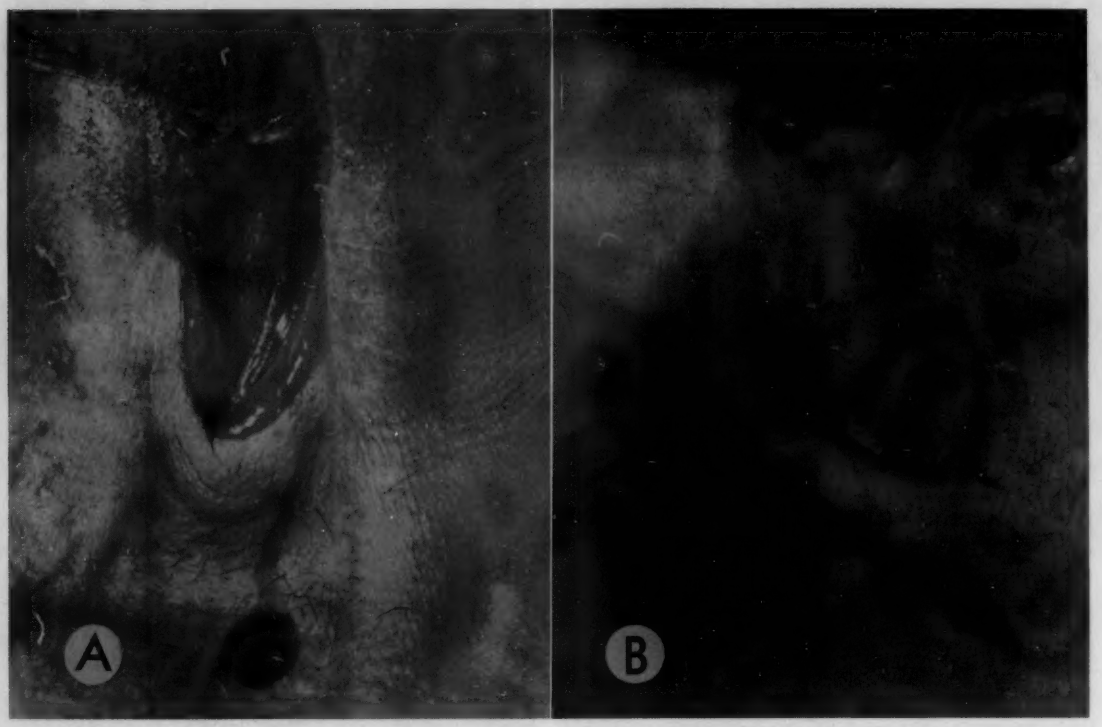

Fig. 8. (*A*) Photograph showing the pharyngeal stoma following total laryngectomy, partial pharyngectomy and right radical neck dissection. *B* shows tube graft built for repair of the stoma.

August 31 to October 30, 1953. The surgical specimen was reported as showing squamous cell carcinoma, Grade III, of the left pyriform sinus with perforation and destruction of the left thyroid cartilage and extension into the intrinsic larynx at the level of the cricoid cartilage. The patient has remained free of disease for seven years.

Patients with squamous cell cancer of the paranasal sinuses (ethmoid, sphenoid, antral and frontal) comprise a group with a poor prognosis. For several years a program of postoperative radiation therapy had been carried out at the M. D. Anderson Hospital following the classic radical resection of the superior maxilla with curettage of the ethmoids and sphenoid and exenteration of the orbit. The results were only slightly better than with resection alone. In the past two years, the treatment procedure

Fig. 9. Photograph of patient shown in Figure 8 taken six years after admission showing completion of closure of the pharyngeal stoma.

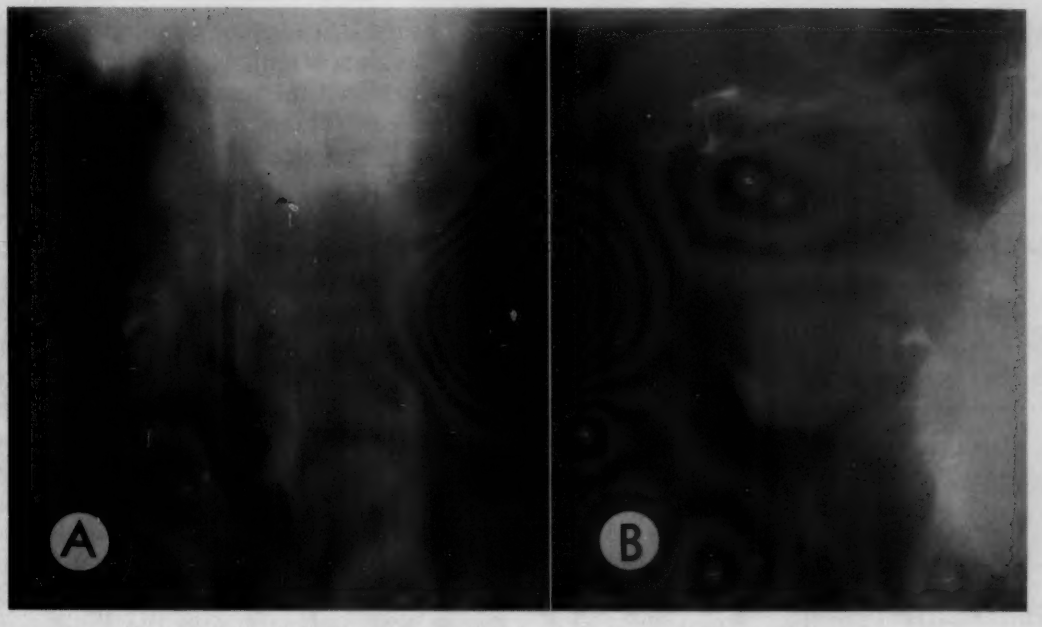

Fig. 10. (*A* and *B*) Roentgen studies showing extent of disease of the larynx.

has been reversed and the radiation therapy has been given preoperatively. The consensus now is that the patient's postoperative course is more turbulent with this technique. Also, skin grafts, though they seem to have taken well during the first two weeks, later tend to separate and slough off from the irradiated field. However, some improvement in the end results has been noted. More time is needed to determine the advisability of continuing with the present program.

SUMMARY

Tables have been compiled to show the distribution of various anatomic cancers of the head and neck region treated during the past eight years at M. D. Anderson Hospital by combined use of radiation therapy and surgical procedures. Planned and unplanned courses of therapy have not been tabulated separately. The number and survival rate of patients with cancer of the oral cavity, oropharynx and larynx, treated by resection plus radiation therapy, and by radiation plus surgical procedures, are shown in Table II. The total number of patients treated by combined therapy, regardless of whether they had received treatment previous to admission to M. D. Anderson Hospital, is shown in Table III.

CONCLUSIONS

In 1906, Crile stated that cancer in the head and neck areas infrequently resulted from distant metastases but more often from uncontrolled local or regional metastases. Fifty years later that statement is still true, but to a lesser degree. Primary early cancer of the head and neck may be controlled by either radiation therapy or by surgical procedures, depending on the site and extent of the lesion. The public and the medical profession are not yet fully alert to the urgency for early diagnosis of cancer of the head and neck regions. Many of these cancers are easily accessible and completely manageable before regional metastases have developed. For the more advanced lesions, both radiation therapy and surgical procedures are often necessary in order to obtain the optimal results. To accomplish this most effectively, a closer liaison between the two specialties is needed. Too frequently, the therapist and the surgeon are not fully cognizant of what can be ac-

TABLE II

SURVIVAL RATE OF PATIENTS TREATED ONLY AT M. D. ANDERSON HOSPITAL

Site	No. of Cases	Survival after Treatment (yr.)	Survival Rate*	Standard Error†
Oral Cavity	130	1	83.5	3.2
		2	64.2	4.4
		3	*55.5*	*4.9*
		4	49.0	5.3
		5	*49.0*	*5.3*
Oropharynx‡	78	1	80.5	4.5
		2	57.5	5.7
		3	*46.5*	*5.9*
		4	40.6	6.0
		5	*40.6*	*6.0*
Extrinsic Larynx (supraglottic and pyriform sinus)	43	1	83.7	5.6
		2	69.7	6.9
		3	*60.4*	*7.4*
		4	50.7	7.6
		5	*41.2*	*7.9*
Intrinsic Larynx	22	1	77.3	8.9
		2	77.3	8.9
		3	*63.2*	*10.3*
		4	52.7	10.9
		5	*52.7*	*10.9*

complished by the other's modality. Should one individual attempt to specialize in both modalities in the treatment of head and neck cancer? This would be the ideal solution but in practice it becomes impractical, if not impossible. The requirements of the specialty boards for a number of prescribed years of training for certification prohibit one individual from acquiring more than one specialty in this present day. What then can be the solution? Institutions giving postgraduate training in each specialty should make a provision for trainees to spend at least six months on the other service in order to familiarize themselves with the end results obtained by the other modality. In order to accomplish fuller coordination between services, the patients should be seen and followed by each. By recognizing and accepting the limitations

* Cumulative survival rate according to Berkson and Gage.[2] Three and five year results are italicized.

† Standard error according to Greenwood.[11]

‡ Oropharynx includes palatine arch (soft palate, anterior tonsillar pillar and retromolar trigone) and pharynx (faucial tonsil, base of tongue and pharyngeal wall).

TABLE III

CANCERS OF THE HEAD AND NECK TREATED BY COMBINED THERAPY

		No. Treated before Admission to M. D. Anderson Hospital	No. Treated at M. D. Anderson Hospital Only	
			Surgery and Radiation	Radiation and Surgery
Oral Cavity	floor of mouth	9	3	38
	buccal mucosa	20	1	12
	tongue	30	5	64
	gum	28	14	13
Oropharynx	soft palate	0	2	8
	retromolar trigone	2	3	17
	tonsil	2	1	18
	pharyngeal wall	10	0	9
Larynx	intrinsic	19	17	5
	extrinsic	23	38	5
Total		143	84	189
Combined Total				416

and advantages of each modality, the best may be achieved by both.

The University of Texas
M. D. Anderson Hospital and Tumor Institute
Houston, Texas

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RADIATION THERAPY IN THE MANAGEMENT OF NEOPLASMS OF THE CENTRAL NERVOUS SYSTEM, WITH A SPECIAL NOTE IN REGARD TO CHILDREN: TWENTY YEARS' EXPERIENCE, 1939–1958*

By JEAN BOUCHARD, M.D., D.M.R.E. (Cantab.),† *and* CARLETON B. PEIRCE, A.B., M.D., M.Sc., F.R.C.P.(C), F.A.C.P., F.A.C.R.‡
MONTREAL, QUEBEC, CANADA

PERIODIC review of experience, with associated critical assessment of effectiveness, is imperative in the use of ionizing radiation as a therapeutic agent. In no group of malignant tumors is this more true than in regard to those arising in the central nervous system, especially within the brain and brain stem. Their biologic characteristics, as well as their common location in critical areas, increase the difficulty of diagnosis and of surgical extirpation. The potential role of radiation therapy in the control of these neoplasms, either conjointly with surgery, or alone when surgical measures are incompatible with preservation of function or life, should be constantly under scrutiny.

Disability and mortality are common effects of these tumors, which influence notably cold statistical analysis of results. Whether or not irradiation will favorably affect either or both the virtually inherent disabling or lethal characteristics of these neoplasms must be continually and critically applied. These questions can be answered only by a long-term project such as is now reported.

Some types of neoplasms of the central nervous system are so exotic that few diagnostic and therapeutic groups will have opportunity to accumulate a statistically significant number for study.

During the twenty year period, 1939–1958, we have treated with ionizing radiation a substantial number and variety of neoplasms of the central nervous system. This has resulted from our close association with the Departments of Neurology and Neurosurgery of the Montreal Neurological Institute and the Royal Victoria Hospital. The patience, interest and cooperation of our colleagues in those fields is gratefully acknowledged. Only under such auspicious circumstances, with their very close observation and response to the patient's often critical requirements for medical and nursing care, could we have persevered and obtained the results which will speak for themselves.

Evaluation of the effectiveness of radiation therapy in the management of tumors of the central nervous system must be closely related, in general, to the individual differences of each type of tumor treated. Classification of these neoplasms rests primarily on their histopathologic features which often present difficult problems to the neuropathologist. During the winter 1958–1959, many hours were spent discussing with the late Doctor William V. Cone his review of the histopathology of the entire group in order to accomplish a special re-analysis of the clinical and histopathologic features of these tumors. This applied particularly to certain tumors which had behaved peculiarly and others whose classification had been rather obscure.

As a result of that review of the more than 800 cases in our entire series of 1939–

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† Radiologist-in-Charge of the Therapeutic Division of the Department of Radiology, Royal Victoria Hospital and Consultant in Radiation Therapy at the Montreal Neurological Institute.

‡ Radiologist-in-Chief of the Royal Victoria Hospital and Consultant Radiologist at the Montreal Neurological Institute.

1958, some have been re-classified histologically. The distribution by kind of neoplasm, therefore, varies slightly from our previous last reports to the Inter-American Congress in 1955 and the VIIIth International Congress of Radiology in 1956.

In this re-study of the cellular characteristics and clinical manifestations, there emerged some further clarification of the behavior of some types of tumors.

CLINICAL MATERIAL

Eight hundred and twenty-six patients comprise the entire series of tumor cases involving the central nervous system for the twenty year period 1939–1958, inclusive. There were 63 patients (less than 8 per cent during the entire period) on whom irradiation was initiated but who, for various reasons, were irradiated either hardly at all, having received only a few treatments, or inadequately for any possible valuable effect and who, for all practical purposes, should be considered as untreated or treated surgically only.

The 763 who were *adequately irradiated* (*i.e.*, received a tumor dose within the range of dose-time relationship which could be expected to be potentially capable of controlling the neoplastic process and possibly accomplish a curative effect) include 229 who have been so treated during the last five years.

During the period 1939–1953, radiation therapy was initiated on 586 patients with neoplasms involving the central nervous system. Five hundred and thirty-four of these were *irradiated adequately* and had an opportunity to live more than five years since diagnosis and initiation of that radiation therapy (Table 1).

These present an unselected, *adequately treated* series in which are included all those patients who have received severally 50 per cent or more of an amount of radiation considered by us as adequate (in terms of time-dose relationship) in the management of such tumors.

For the purpose of this report, the major discussion will be devoted to the analysis of the apparent clinical results of irradiation in the treatment of the 399 patients affected with primary intracranial tumors.

Some discussion will be devoted to the use of irradiation in the palliative control of selected cases of brain metastases. Inasmuch as the history has now been completed on all of the 29 who were treated in the twenty-year span, assessment of the effect of the treatment of these can be made at this time.

Special consideration will be given to the 79 children (under fifteen years of age) who are included in the series of 399. This will afford useful information for future guidance in the management of brain tumors in a group of patients generally considered to be of critical age for irradiation of their skull and intracranial content.

The pituitary tumors and the spinal cord neoplasms will be reserved for separate communications.

TABLE I

NEOPLASMS OF THE CENTRAL NERVOUS SYSTEM

(*Adequately irradiated*)

Clinical Material	No. of Patients		
	1939–1953	1954–1958	Total
Primary intracranial tumors	399	167	566
Metastases to brain	19	10	29
Pituitary tumors	82	30	112
Spinal cord neoplasms	34	22	56
Total	534	229	763

The program of radiation therapy has been consistently that of a *single protracted series* of treatments via multiple portals over a period of approximately fifty days, designed to accumulate on the average a total tumor dose of 5,000 to 6,000 r generated at predominantly 220 to 280 kv.

In our previous reports, mention has been made of the trial of larger doses in selected cases, especially regarding glioblastoma multiforme. Those were intentional exceptions from which we have gained sufficient experience to consider now that the biologic effect of the above dose-time relationship will probably induce as good a result as can be expected with ionizing radiation.

Some of the later cases in the twenty year series have been treated with the cobalt 60 beam on a similar program. Although for equivalent dosage, no specific difference in biologic effect on similar tumors has been observed, insufficient time has elapsed since 1955 to permit full assessment of this medium.

CLASSIFICATION

Of the 1939–1953 group of 399, 78.5 per cent are now classified as gliomata. For purposes of this analysis, 298 cases of gliomata, consisting of the first six groups shown in Table II, can be considered best under their individual histopathologic classification. The mid-brain and pontine tumors, although we now have histopathologic identification in 12 of the 41 (11 of which are gliomata), form a separate group, largely because of their location and the frequent difficulty to procure even biopsy material. The "miscellaneous" group also contains 4 gliomata, but the number of any specific type of tumor in these 17 cases is too small to permit analysis of behavior under irradiation as specifically characteristic of its cell-type.

The meningeal tumor, the sarcoma and the angioma-hemangioblastoma groups present different natural histories and factors of response to irradiation which separate them from the common herd.

As we have indicated in the preamble, some tumors present difficulty in absolute classification histologically. The nomenclature applied in individual cases here has been the result of much consideration and discussion by and with our colleagues, Dr. Arthur Elvidge, the late Dr. W. V. Cone and others. This applies particularly to the

Table II

CLASSIFICATION OF PRIMARY INTRACRANIAL NEOPLASMS

(*Adequately irradiated*)

Type or Location	No. of Cases		
	1939–1953	1954–1958	Total
Glioblastoma	125	48	173
Astrocytoma	81	45	126
Glioma—unclassified	30	7	37
Medulloblastoma	41	9	50
Ependymoma; blastoma	12	2	14
Oligodendroglioma; blastoma	9	5	14
Mid-brain and pontine tumors	41	26	67
Meningeal tumors	16	9	25
Sarcoma	13	4	17
Angioma; hemangioblastoma	14	1	15
Miscellaneous:			
Histologically classified	14	11	25
Histologically undetermined	3	0	3
Total	399	167	566

sorting out of the ependymal tumors, medulloblastomas and sarcomas.

At the present writing, there remain but 32, or 8 per cent of the primary neoplasms in which histologic identification has not been possible by operation, biopsy or autopsy. Nine of these are still alive; 8 of them belonging to the mid-brain and pontine group.

Thanks to the diligent and devoted work of our secretarial and follow-up staff, the clinical story is complete to date on 99.52 per cent of the patients with primary intracranial neoplasms. We have no follow-up in only 3 of those 399 patients.

RESULTS OF TREATMENT OF THE PRIMARY INTRACRANIAL NEOPLASMS

Statistical analyses of results of treatment of neoplastic diseases are traditionally presented according to the length of survivals. This is usually valid. However, in dealing with intracranial neoplasms, survival rates are truly valuable only insofar as the majority of the patients surviving are capable of resuming an active useful life, with only a small percentage of them remaining totally incapacitated (Table III).

The length of survival has been calculated in all cases from the first day of radiation therapy. The few cases which have remained untraced have been considered as deceased due to their tumor within the first twelve months following treatment. No allowance has been made for correction because of death resulting from unrelated disease or accident (Table IV).

Eighty-nine, or 22.3 per cent of the 399 patients irradiated for various types of primary intracranial tumors are still living,

TABLE III

QUALITY OF SURVIVAL OF 315 PATIENTS WITH GLIOMATA

75.6%	resumed active useful life
18.5%	had partial disability, but were not incapacitated
5.8%	were totally incapable of self care

TABLE IV

LENGTH OF SURVIVAL OF 399 PATIENTS WITH PRIMARY INTRACRANIAL NEOPLASMS

32.8% or	131/399 have lived over 5 years
24.0% or	58/242 have lived over 10 years
17.0% or	17/100 have lived over 15 years

five to twenty years after irradiation. Of those who are now deceased, 42, or 10.5 per cent lived more than five years after irradiation, making up the total of 131, or 32.8 per cent who survived five years or more after diagnosis and treatment.

The majority of patients (88 per cent) have been treated postoperatively, chiefly because of presumably incomplete removal of tumor. Only a few were referred for postoperative irradiation following an apparently complete surgical removal of tumor. In this group are included a small number who were irradiated after they developed definite evidence of postoperative recurrence of tumor.

The remaining 12 per cent, consisting largely of mid-brain or pontine tumors, some of the medulloblastomata, sarcomata and angiomata, were treated by irradiation alone without any attempt at surgical removal of the tumor. Some of these had had a craniotomy for various purposes such as biopsy, attempt at removal or decompression with or without shunt, but without significant ablation of tumor.

The ten year life expectancy in each group of neoplasms is a true survival rate for the groups treated during 1939–1943 and 1944–1948, since it is established on the percentage of patients who have actually survived ten years or more. This can be applied as an actuarial estimate of probable ten year survival (based upon the experience with the previous two groups) of the patients treated between 1949–1953 and surviving five to ten years after irradiation.

With these general observations in mind, the particular characteristics and results in regard to the individual type or group of intracranial tumors can be considered in some detail.

TABLE V

GLIOBLASTOMA MULTIFORME

Life Expectancy Dependent upon Treatment		
Period of Time	Surgery Only*	Surgery and Irradiation†
Over 1 year	31.8%	39.0%
Over 2 years	6.5%	20.0%
Over 3 years	—	11.2%
Over 5 years	—	7.2%‡
Over 10 years	—	4.0%

* Elvidge, Penfield and Cone:[8] 27 cases, 1935 report.
† Present series: 125 cases, 1939–1953; follow-up complete.
‡ In view of the survival of an appreciable number over five years, all 9 of those cases were reviewed and the histopathology confirmed.

GLIOBLASTOMA MULTIFORME

Glioblastoma multiforme is recognized generally as having the poorest prognosis of all the malignant gliomata. Bailey[2] suggested fifteen months as the probable maximum life expectancy. Twenty per cent of our cases lived more than two years. Of the group of 125, all of whom had a possible chance to live five to twenty years, 4 (3.2 per cent) are still alive, seven, nine, eleven and fourteen years since diagnosis and initiation of treatment (Table v).

In comparison with the earlier surgical series reported by our colleagues in the Institute, just prior to the beginning of our series, although surgical techniques have advanced markedly since that time, the combination of irradiation with surgery, as in our 125 cases, offers a definite advantage.

ASTROCYTOMA

The astrocytomas present a markedly different and more favorable pattern, largely due to the character of that neoplasm and its natural history. Comparison of life expectancy, based on the actual survival of patients in our series of 81 cases treated from 1939 to 1953, with a series of 71 cases treated with surgery alone between 1940 and 1949 (Levy and Elvidge[12]) shows that the patients treated with *surgery and irradiation* may expect a much greater longevity (Table VI).

Fifteen of these patients have lived over ten years since initiation of their treatment. Ten of them are still living with an average attained longevity of 162 months (13.5 years). The average survival of the 5 who have died after ten years was 13.4 years after treatment; the 4 of the 10 who are still living over ten years have passed the 15.3, 15.6, 17.3 and 18.0 year points, respectively.

TABLE VI

ASTROCYTOMA

Life Expectancy Dependent upon Treatment		
Period of Time	Surgery Only*	Surgery and Irradiation†
Over 3 years	59.0%	61.7%
Over 5 years	38.2%	49.3%
Over 6 years	26.8%	46.9%
Over 10 years	—	35.8%

* Levy and Elvidge:[12] 71 cases, 1940–1949.
† Present series: 81 cases, 1939–1953; follow-up complete.

Although there may be some differences in the natural history of the several types of astrocytomas, as indicated in Martinez-Coll's and Levy's respective papers with Elvidge,[10,12] we have previously examined the results in the irradiated group of astrocytomas, sorted by cell type, with the conclusion that, in the long view, no significant variation in tumor response or length of survival appears between these subgroups.

UNCLASSIFIED GLIOMATA

The unclassified gliomata (30 cases) respond slightly less well than the astrocytomas, with a life expectancy as reflected in their survival rate shown in Table VII.

TABLE VII

UNCLASSIFIED GLIOMATA*

Life Expectancy	Surgery and Irradiation
Over 1 year	66.0%
Over 2 years	50.3%
Over 3 years	40.0%
Over 5 years	30.3%
Over 10 years	20.0%

* Present series: 30 cases, 1939–1953; no follow-up on 1 case.

MEDULLOBLASTOMA

The medulloblastomas also have been critically reviewed histologically within the past year, with the result that several cases were lifted out of the medulloblastoma group to be re-classified mostly with the cerebellar sarcomas. In view of the generally held concept of the ability for medulloblastomas to metastasize along the cerebrospinal spaces, the entire cerebrospinal axis has been irradiated in practically all our cases. However, we are inclined to doubt that dissemination along the spinal axis is as constant a characteristic of this tumor as generally believed. Only 5 (12.2 per cent) of our series had involvement of the spinal axis. None of these were of the group which had been subjected to only aspiration biopsy prior to irradiation. Metastasis by medulloblastomas to other parts of the body outside of the cerebrospinal axis has not been observed in our series.

Although the over-all longevity rates in our group of 41 cases of medulloblastoma appear to be rather favorable (Table VIII), they are markedly less so than the results published by Paterson and Farr[13] with a series of 27 patients irradiated between 1941 and 1950. They have reported a three year survival rate of 65 per cent, whereas ours is only 29.2 per cent. The classification of tumors and the conditions may be different between the two series.

It is of interest to note that of the 6 of our 41 patients who were subjected only to biopsy before roentgen irradiation, 2 are alive now more than ten years after treatment.

EPENDYMOMA AND EPENDYMOBLASTOMA

Certain other types of gliomata are not sufficiently frequent to allow for extensive experience in their management. Their respective numbers being relatively small, it is fully realized that instead of valid statistics only an outline of a pattern, based upon results of treatment, may be derived from the analysis of these. This applies to our series of ependymomas and ependymoblastomas, as well as to oligodendrogliomas and oligodendroglioblastomas.

Ependymomas and ependymoblastomas were involved in 12 cases treated with surgery and postoperative irradiation in the present series. Ependymal tumors have been reported to disseminate along the cerebrospinal axis in the same way as medulloblastomas. Irradiation of the axis has been advocated. We have not made a practice of such plan of treatment. The entire cerebrospinal axis was irradiated in only 1 of our 12 cases. Clinical evidence of such type of neoplastic dissemination has not been observed in any of our 12 patients, although there has been ample time for such manifestation to develop, since 9 patients lived more than three years after treatment. Long survivals would seem to be the pattern with these tumors. Five of the 6 patients still living have survived more than ten years after irradiation, and 4 of them over fifteen (Table IX).

TABLE VIII

MEDULLOBLASTOMA*

Life Expectancy	Surgery and Irradiation or Irradiation Alone
Over 1 year	63.4%
Over 2 years	39.0%
Over 3 years	29.2%
Over 5 years	19.5%
Over 10 years	14.6%

* Present series: 41 cases, 1939–1953; no follow-up on 1 case.

TABLE IX

EPENDYMOMA AND EPENDYMOBLASTOMA*

Life Expectancy	Surgery and Irradiation
Over 1 year	83.3%
Over 2 years	75.0%
Over 3 years	75.0%
Over 5 years	58.3%
Over 10 years	50.0%

* Present series: 12 cases, 1939–1953; follow-up complete.

OLIGODENDROGLIOMA AND OLIGODENDROGLIOBLASTOMA

These tumors are even more uncommon types of gliomata. Slowly growing and usually sufficiently well circumscribed to be amenable to complete surgical removal, long uneventful survival is frequent. Our case material is comprised of only 9 cases, which were irradiated either because of more malignant character than usual or in view of definitely incomplete surgical removal (Table x).

TABLE X

OLIGODENDROGLIOMA AND OLIGODENDROGLIOBLASTOMA*

Life Expectancy	Surgery and Irradiation
Over 1 year	100.0%
Over 2 years	88.8%
Over 3 years	77.7%
Over 5 years	55.5%
Over 10 years	33.3%

* Present series; 9 cases, 1939–1953; follow-up complete.

Although 5 of these patients survived over five years, only 1 so far has actually lived more than ten years. Two others were reaching seven and eight years of survival after irradiation at our last observation a year ago. No message has been received since of deterioration in their condition, hence a ten year survival probability is assumed in the 33.3 per cent.

MID-BRAIN AND PONTINE TUMORS

The mid-brain and pontine tumors are located in highly critical areas, infrequently accessible even for biopsy, and markedly hazardous to life.

The extent of the hazard to the patient's life is unquestionably related to the location of the new growth. The mid-brain, extending from the posterior portion of the third ventricle down to the protuberance, is the cross-road where nearly all the important motor, general and special sensory nerve fibers converge. The mid-brain also contains the aqueduct of Sylvius which controls the cerebrospinal fluid circulation in the cerebrum itself. Below the protuberance the nerve pathways emerge from the mid-brain into the brain stem or pons through which they link the cerebrum and cerebellum to the spinal cord. Any pathologic process developing in those areas endangers life and may soon be fatal if not corrected.

When expanding lesions arise in the mid-brain or pontine zones, three alternatives present: (1) surgical exploration in an attempt to remove the tumor in part or in whole or even to obtain a biopsy carries an almost prohibitively high mortality risk; (2) masterly inaction will almost surely result in early terminus; or (3) irradiation must be undertaken without histologic confirmation and classification in a large majority.

In our group of 41 of these tumors, the histopathologic type of neoplasm was known, prior to irradiation, in but 7 of the 20 located in the mid-brain, and in only 1 of the 21 pontine lesions. We feel fully justified in irradiating these patients when a firm clinical diagnosis and localization can be established rather than to insist upon pathologic confirmation at the cost of a high mortality rate.

The definitive histopathologic diagnosis of the mid-brain tumors prior to operation or at autopsy so far has included 1 glioblastoma, 1 astrocytoma, 1 ependymoma, 1 medulloblastoma, 2 spongioblastomas, 3 unclassified gliomata and a papilloma of the choroid plexus in the posterior portion of the third ventricle. The pontine tumor was a glioblastoma multiforme.

The results of radiation therapy alone in the initial cases of this series were extremely encouraging and this has gradually led to the adoption of the conservative therapeutic approach.

These are the reasons why we have classified and analyzed the mid-brain and pontine tumors *en groupe* upon the basis of anatomic location rather than on histopathologic type. The results of irradiation presented in Table xi seem to indicate

TABLE XI

MID-BRAIN AND PONTINE TUMORS

(*Adequately irradiated*)

Life Expectancy	Mid-Brain*	Pontine†
Over 1 year	65.0%	62.0%
Over 2 years	45.0%	43.0%
Over 3 years	45.0%	33.0%
Over 5 years	40.0%	33.0%
Over 10 years	25.0%	23.8%

* Present series: 20 cases (irradiation alone in 13 cases), 1939–1953; no follow-up in 1 case.

† Present series: 21 cases (irradiation alone in 20 cases); follow-up complete.

clearly that this approach has been beneficial to the patient.

During the last five years (and therefore not included in the present analysis), 14 additional patients with mid-brain tumors have been treated by means of radiation therapy alone, whereas partial removal of the tumor prior to irradiation was attempted in only 1 other case. This type of conservative management has become possible in the majority of cases because of the facility of controlling intracranial pressure with decompression by means of shunts. These shunts, of several types, permit decompression by diversion of the circulation of the cerebrospinal fluid until gradually it can be restored to normal as the result of shrinkage of the tumor by irradiation.

In this 1939–1953 series of mid-brain tumors, 3 of the 13 patients treated with radiation therapy alone have survived ten years or longer.

The pontine tumors represent a group of cases in which, previously, patients usually have gone untreated and ordinarily were abandoned to a rapid lethal fate. Only 1 of our 21 patients was irradiated prior to 1944. It was really in 1947 that we began to accept the responsibility of treatment of such cases without pathologic diagnosis. We wish to stress that 20 of the 21 patients in this group have been irradiated on the basis of a clinical diagnosis only, and that 4 of them have already survived ten years or longer.

The results of radiation therapy in the management of pontine tumors are particularly striking when we consider that neoplasms in that anatomic location are commonly recognized as inevitably fatal in less than six months from the onset of symptoms.

The possibility that the expanding lesions of the brain stem which we have irradiated might be of non-neoplastic character is very slim. It is known and generally accepted that such lesions nearly always are gliomata, the most frequent types being ependymomas, astrocytomas or glioblastomas. Autopsies performed in 2 of these cases subsequently have confirmed the presence of the glioblastoma multiforme referred to above and one other.

MENINGIOMA

A few intracranial neoplasms other than gliomata have been subjected to radiation therapy with or without previous surgical removal. These include tumors arising from the meninges or the blood vessels and the intracranial sarcomas.

Present practice in this center relies upon surgical removal for the control of benign meningiomas.

Meningiomas which show histopathologic evidence of malignancy are properly malignant meningiomas, but may be subclassified as meningeal fibroblastoma or meningeal sarcoma. The 16 meningeal tumors reported in this series included 12 meningeal fibroblastomas, 2 meningeal sarcomas and 2 ordinary meningiomas which were irradiated postoperatively because of incomplete surgical removal. It is believed that radiation therapy has played a part in the satisfactory survival rates as shown in Table XII. In this small sample, distinction between the fibroblastomas and the sarcomas is impractical.

This experience suggests that the expectancy of life of a patient with a malignant meningeal tumor, who has been treated with surgery and irradiation and has survived three full years afterwards, is such that for all practical purposes he may be

TABLE XII

MALIGNANT MENINGEAL TUMORS*

Life Expectancy	Surgery and Irradiation
Over 1 year	100.0%
Over 2 years	85.7%
Over 3 years	57.1%
Over 5 years	57.1%
Over 10 years	57.1%

* Present series: 14 cases, 1939–1953; follow-up complete.

TABLE XIII

INTRACRANIAL SARCOMAS*

Life Expectancy	Surgery and Irradiation
Over 1 year	77.0%
Over 2 years	61.5%
Over 3 years	53.8%
Over 5 years	38.5%
Over 10 years	30.8%

* Present series: 13 cases, 1939–1953; follow-up complete.

considered as cured, unless recurrence should occur. Three in our series have had recurrence, 2 of whom are still living, fifteen and twelve years respectively after treatment of that complication. The third died twelve years after the treatment of his recurrence.

INTRACRANIAL SARCOMAS

Intracranial sarcomas form a group of primary malignant neoplasms which do not present a homogeneous pathologic entity. In this series are included the perithelial and reticulum cell sarcomas as well as the "fibrous" and other sarcomas of the cerebellum. Nearly all the intracranial sarcomas in this series were located in the cerebellar region. The incidence is relatively high in children: 6 or 46.1 per cent of our 13 cases. In adults, the age group twenty to forty years has been almost exclusively affected.

The pathologic behavior of intracranial sarcomas differs from that of the gliomata and the majority of the other intracranial neoplasms by virtue of their ability to metastasize to other parts of the body outside the central nervous system as other sarcomas may do. We have histopathologic evidence (from autopsies) that not less than 3 of this group of cerebellar sarcomas have metastasized to bones, pleura, peritoneum and abdominal lymph nodes. The peritoneal implant surrounded the end of the ventriculoperitoneal shunt tube.

The management of 11 of 13 cases of intracranial sarcomas has consisted of surgical removal followed with postoperative radiation therapy. The two others were treated with radiation therapy only, following diagnosis by needle biopsy and establishment of shunts. Table XIII shows that the results of treatment are surprisingly better than those which could be anticipated in sarcomatous tumors arising from other structures of the body.

Our only case which presented post-irradiation necrosis of brain appeared in this group. This was a child, five and one-half years of age at the time of her first treatment series, who developed a recurrence five years later, which was retreated. Upon postmortem examination, two years after the second course of irradiation, both hemispheres showed well defined zones of brain necrosis, conforming to the distribution of the opposing lateral supratentorial beams used in the retreatment.

INTRACRANIAL ANGIOMA AND HEMANGIOBLASTOMA

These tumors differ considerably from the other intracranial tumors due to their attenuated course to a disabling or lethal effect, save when they arise from or impinge upon a critical area.

During the period 1939–1953 we have irradiated 14 patients because of blood vessel tumors of various histopathologic types: 8 angiomas, 4 hemangioblastomas and 2 hemangio-endotheliomas. We have yet to see these in children. Our youngest case was seventeen years of age.

The results of treatment, we believe, cannot be judged by the length of survival in any category of the intracranial blood vessel tumors. In this series, as would be

expected, long survivals were common: of 14 cases, 13 have survived over five years, 8 over ten, and 4 more than fifteen years.

Further, of the 4 patients who are now deceased, 3 died of unrelated cause long after treatment. Only 1 died as a result of his hemangioblastoma.

Angiomas are benign vascular lesions apparently resulting from developmental blood vessel anomalies and, as such, are not considered by all as true neoplasms. Often they are called racemose or arteriovenous angiomas. Their structure often resembles that of cavernous hemangiomas elsewhere. Seven of the 8 cases of angioma were located in the cerebrum. Direct treatment of the lesion has consisted of irradiation only in 6 cases, although 3 of them have been explored surgically during a craniotomy for decompression prior to irradiation. Five of those 6 cases are surviving five to eighteen years after treatment, the remaining one having died of unrelated disease 139 months after treatment.

Of the 2 patients treated with partial surgical removal and irradiation, 1 has now lived 85 months while the other died of unrelated disease 139 months after treatment.

The dose of radiation required in the treatment of cerebral angiomas does not need to be as large as that employed for the gliomata, etc. We believe that a maximum tumor dose of 3,500 r over a period of thirty to thirty-five days should be adequate and this has practically never been exceeded in the present series.

Hemangioblastomas, on the other hand, represent true neoplastic processes, but of low grade malignancy. Most of these neoplasms are fairly well demarcated and grow within a cyst. Histologically they are formed of over-abundant capillaries and more or less cystic vascular spaces containing blood with strands of endothelial cells lying between them. Hemangio-endotheliomas are a variant, the basic cell of which is also endothelial in origin with proliferation of capillaries of a more or less invasive character. The tumor will consist of variable quantities and arrangement of the endothelial elements, capillaries, more or less cystic blood-filled spaces and cysts containing fluid (probably derived from old blood), with often nodular tumor masses in the periphery of the cysts.

The 4 hemangioblastomas involved either the cerebrum (1) or the cerebellum (3). The dominant incidence of such tumors in the cerebellar region may be on an embryologic basis. Partial surgical removal followed by irradiation was the treatment in 3 patients, of whom 2 are surviving after 173 to 220 months. One died during a second operation, for recurrence, 50 months after initial treatment. The remaining patient is alive but nearly blind, 70 months after surgical exploration and irradiation.

Treatment of the 2 cases of hemangio-endothelioma, both involving the cerebellum, consisted of incomplete surgical removal and irradiation. The first died of unrelated disease 196 months after treatment. No residual tumor was found at autopsy. The second is alive and well 93 months after treatment.

The hemangioblastomas, because of their potential malignant character, have been treated with tumor doses varying between 3,000 and 5,000 r in thirty-five to forty-five days. Because of their more malignant character, the hemangio-endotheliomas have been given tumor doses of the order of 5,000 to 6,000 r over a period of forty-five to fifty days.

The quality of survival may be a better criterion for evaluation of results than the length of survival.

All 8 cases of angioma had good useful survival without significant disability. Relief of symptoms and early signs of regression of the lesion were becoming manifest six to twelve months after completion of irradiation. In the majority of cases all symptoms and clinical signs seemed to have subsided within two years of treatment.

The cases of hemangioblastoma and hemangio-endothelioma presented more distressing symptoms and more severe neuro-

logic signs on admission. This was probably due to the more common subtentorial location. Four of them have made a good recovery following surgery and irradiation. Three became completely symptom-free. The other resolved to a stage of minor disability, not sufficient to prevent him from working during the nearly four years which elapsed between irradiation and his death at operation for a recurrence. Two patients have not been able to return to employment after treatment because of residual disability, but were able to care for themselves.

Objective assessment by arteriography of the effect of treatment would be desirable in the case of angiomas approximately two years after irradiation. This could demonstrate the gradual obliteration of the lumen of blood vessels and probably determine the extent of regression of the lesion.

This method of evaluation of therapeutic management would be valid, however, in probably less than 50 per cent of the cases of hemangioblastoma and hemangio-endothelioma because not more than such a proportion of these could be demonstrated by arteriography, either before or after surgery and irradiation.

Because of the predominant cerebellar location, the necessary vertebral artery angiogram interposes some technical difficulties. For these and a number of fairly valid reasons, such follow-up arteriography has not been practicable here. To the best of our knowledge, there is virtually no information available from other centers in that respect in the current literature.

MISCELLANEOUS PRIMARY INTRACRANIAL NEOPLASMS

This group included 17 patients upon whom a diagnosis of primary brain tumor was made. All were treated with a combination of surgery and irradiation.

The histologic type of neoplasm was determined in 14 cases: 4 astroblastomas, 3 chordomas, 2 craniopharyngiomas, 2 medulloepitheliomas, 1 neuroepithelioma, 1 perineurial fibroblastoma and 1 congenital brain cyst (heterotopia). The number of each is not sufficient at this time to warrant any valid comment as to respective type behavior as a result of irradiation. This heterogenous agglomeration of cases accounts, as shown in Table IV, for 7 five year, 4 ten year and 2 fifteen year survivals.

The histologic type of tumor was not determined in 3 cases in which a final diagnosis of intracranial neoplasm had to be made on clinical grounds only. Surgical exploration and attempt at aspiration biopsy had failed to establish the exact nature of the expanding lesion. The 3 patients were irradiated postoperatively on the assumption that they had brain tumors because of the clinical signs and symptoms. Two of them died six and twenty-six months after treatment with continuing clinical signs of intracranial neoplasm. Postmortem examination was not permitted on either. One is alive and well 58 months after irradiation.

RESULTS OF TREATMENT OF METASTASES TO THE BRAIN

The apparent increasing frequency of identification of metastases to the brain, predominantly from visceral primary malignant neoplasms, presents a very real clinical problem. Twenty-seven patients with metastatic lesions in the brain or brain stem were accepted for irradiation during the twenty years under review; 17 during the first fifteen years (1939–1953).

Inasmuch as the history of the 10 who were treated during the later period (1954–1958) is now also a "closed chapter," discussion of the whole group seems appropriate. Two eosinophilic granulomata involving the brain by extension respectively from the middle fossa and the base of the skull have been added to this group only for purposes of record.

Not uncommonly the presence of an expanding intracranial lesion is indicated before the primary tumor is suspected or found. Although the identity of the source may be suspected from a careful medical history, the metastatic lesion is frequently

undistinguishable by its symptoms and signs from any other intracranial tumor, and often remains unrecognized clinically until fairly late.

Seven patients (25.9 per cent) of the group were initially referred with diagnoses severally of one of the primary intracranial tumors and so treated (Table XIV). Three were subsequently identified in the course of surgical intervention. The true diagnoses of the other 4 were not discovered until autopsy.

Whether or not relief or improvement of the mental and physical condition of these patients can be accomplished, despite the known probability of metastasis, is a question which commonly must be answered by the attending physician or surgeon and his consultants. Prolongation of extended useful life is less probable under these circumstances than with metastasis elsewhere. Nevertheless, resumption or any gain of conscious and useful life may be a material boon to both patient and family. Twenty (74.07 per cent) of these patients returned to an essentially normal condition clinically in respect to their symptoms and signs of intracranial involvement. We had little information on the subsequent clinical course of 3, but the remaining 17 enjoyed that quality of improvement for the major portion of their subsequent survival period. Five showed an excellent response. Only 7 of the entire group showed no improvement.

Because of the variety of tumor types, rapidity of growth and location of the implants, as well as the wide diversity in extent of metastatic involvement elsewhere in the patient's body, the result of irradiation in terms of either duration of life or quality of improvement is variable. Nevertheless, we have observed dramatic return of both mental and physical function in two-thirds of these patients. We therefore consider that measures to induce even short resumption of useful, conscious life are worth while.

Differentiation of the metastatic tumors from primary intracranial malignancies is more difficult when there is but one large mass. In the presence of multiple intracranial implants, the signs become more complex or confused. Under such circum-

TABLE XIV

METASTASES TO BRAIN

1939–1958

Primary Source	Diagnosis at Time of Initiation of Treatment
8 Carcinoma, bronchogenic	1 ependymoma; 1 glioblastoma; 1 astrocytoma; 5 primary previously or concurrently diagnosed
5 Carcinoma, mammary	1 astrocytoma; 4 previously known primary
1 Carcinoma, rectum	meningeal fibrosarcoma
3 Carcinoma, testis	1 previously known; 1 undetermined; 1 meningeal sarcoma
1 Carcinoma, thyroid	glioblastoma multiforme
1 Carcinoma, hypernephroid	previously known primary
1 Dysgerminoma	medulloblastoma
3 Melanocarcinoma	primary lesions of foot and back—previously known
4 Primary (undetermined)	1 perithelial sarcoma; 1 glioma; 2 intracranial unidentified tumors

stances, sometimes with particular assistance from electroencephalography, the probability of metastatic disease must be considered and at times accepted without proof as the basis for decision as to management.

Seven of the 20 cases which were accepted and treated as intracranial metastases solely on the basis of the clinical diagnosis were not subsequently confirmed by autopsy or biopsy. Seven were identified by craniotomy and 2 by needle biopsy prior to irradiation. The other 4 were not confirmed until autopsy.

Selection must be based upon (1) knowledge of the known or probable primary tumor; (2) whether or not the primary tumor is under control and whether this is probably the only intracranial implant (although final data frequently show that the metastases to the brain are multiple); or (3) if the primary tumor is not under control, whether there are other metastases but none which are endangering vital organs; and (4) a reasonable chance that, if the intracranial tumor can be controlled, the patient may achieve a relatively useful survival period.

The question will repeatedly present as to whether or not the lesion is singular. Unless signs and other evidence indicate definitely focal direction of therapy, irradiation of the whole cranial content should be employed because of the hazard of multiple implants. The dose-time relationship will have to be gauged according to the nature of the primary tumor as well as to be consonant with good practice regarding treatment of the brain or brain stem.

One barrister, with metastases from a carcinoma of the testis, was treated on four occasions over a total survival period just short of nine years. His initial remission of symptoms and signs after treatment of his first metastasis lasted five years, and the second nineteen months. All in all, he was able to carry on a major portion of his legal practice, enjoy his family and his community interests for over seven of those years.

A girl, whose ovarian tumor was not found until forty-four months after discovery and treatment of the initially unidentified cerebral metastasis, was free of signs and symptoms of the intracranial lesion until three months before her death from generalized metastasis of the dysgerminoma, four and one-half years after the first treatment.

Another man with an unidentifiable primary tumor lived eighty-five months, a fourth with bronchogenic carcinoma thirteen months and 11 others six to thirteen months after treatment.

These were some of the more fortunate ones. A large majority have been restored to sufficient well-being to care for themselves for a fair amount of their "borrowed time."

We therefore believe that there is a definite role for radiation therapy in the management of selected cases of intracranial metastases.

PRIMARY INTRACRANIAL NEOPLASMS IN CHILDREN

When, in a child, the diagnosis of brain tumor is made, great concern arises as to the immediate prognosis and the potential remote sequelae in the event of survival. In each case, the therapeutic management will be greatly influenced by the relative morbidity attributed to the suspected or known type of neoplasm and the location of the tumor in the brain or brain stem. The comparative hazards of treatment by surgical approach or by irradiation, used separately or jointly, will be carefully appraised. Life expectancy of this particular age group, relative to each modality of treatment, estimated in terms of both the length and the quality of survival, will be a further essential consideration in arriving at a decision in the individual case.

Data on the results of surgical management of brain tumors in children have been published by others. These apply particularly to the "benign" types, which Horrax[11] qualifies as "favorable" tumors because they usually can be extirpated *in*

toto by surgery. In children, the "favorable" tumors consist chiefly of the cystic cerebellar astrocytomas and the few hemangiomatous cysts. We have not used postoperative irradiation in such cases.

Since the central nervous system is believed to not complete its development before the age of fifteen, exposure to ionizing radiation in the dose levels required and used in this series of intracranial neoplasms generally has been considered particularly hazardous for all children up to the age of fifteen.

Our current twenty year experience with irradiation of intracranial neoplasms embraces the treatment of 120 children under fifteen years of age. The present discussion will be restricted to the 79 whom we irradiated during the period 1939 to 1953, and who have had a potential survival of five to twenty years. This special segregation of cases has been made in order to obtain some particular evaluation of the effects of irradiation of the central nervous system in the young.

In this series the proportion of children, aged fifteen years or less, to that of older adolescents or adults irradiated for primary intracranial tumors is practically one to four (79:320).

Classification of this clinical material according to the type of neoplasms or their location in the brain and brain stem is shown in Table xv.

Comparison of the last two columns of Table xv indicates those types of tumors which are relatively more common in adults than in children. Only the medulloblastomas have a greater incidence in children than in adults, with a per cent of 68.3 of the 41 medulloblastomas in the total series. As a corollary, but 35.5 per cent of the cases of intracranial neoplasms in children which we have irradiated were medulloblastomas.

The several groups of intracranial neoplasms which are not mentioned specifically in Table xv included 193 patients in the entire 1939–1953 series, whereas only 8 of them were children. These young people were irradiated for the following histopathologic conditions: 1 glioblastoma multiforme, 2 ependymomas, 1 meningeal fibroblastoma, 1 astroblastoma, 1 medulloepithelioma, 1 neuroepithelioma and 1 craniopharyngioma. No oligodendroglioma or blood vessel tumor was seen in this group of children.

The age distribution in this series of 79 children, whose skulls and intracranial contents have been irradiated for intracranial malignant neoplasm, is fairly uniform: 28 from six months to five years of age; 28 from six years to ten; and 23 from eleven to fifteen, inclusive.

Table XV

PRIMARY INTRACRANIAL TUMORS IN CHILDREN AGED FIFTEEN OR LESS*
CLASSIFICATION BY TYPE OR LOCATION AND INCIDENCE

	No. of Children	Per Cent Incidence in Children's Series	Per Cent Incidence of Children by Type in Total Series
Astrocytoma	12	15.2	14.8
Glioma Unclassified	9	11.4	30.0
Medulloblastoma	28	35.5	68.3
Mid-Brain Tumors	7	8.8	35.0
Brain stem Tumors	9	11.4	43.0
Sarcoma	6	7.6	46.1
All Others	8	10.0	4.1
	79	100.0	

* Present series: 79 children (19.7 per cent) among 399 patients *adequately irradiated*, 1939–1953. Follow-up complete, except for 1 medulloblastoma.

Only the children whose malignant intracranial tumor could not be extirpated completely at operation or could not be removed at all have been irradiated.

In 27.8 per cent, or 22 of the 79 children, there was no surgical removal, although 4 were explored surgically and shunts established in 2 of the 4. Consequently, irradiation may be considered the only active treatment of these 22 patients. The histopathologic diagnosis was not established at time of treatment in 14 of the 22 cases whose several tumors involved the midbrain in 3, the brain stem in 9. Subsequently, 2 more were identified, 1 as a medulloblastoma, the other as a sarcoma. In the remaining 8 children (who received irradiation alone) the true histologic diagnosis had been determined from material obtained by needle biospy (6 medulloblastomas and 2 sarcomas).

The histology had been established at operation in the 57 children who had had partial removal of their neoplasms.

The *program of radiation therapy* in children has been nearly identical to that used in adults. The tumor doses for the children usually have been less by a factor of 20 per cent, approximately. Accordingly, average tumor doses of 4,500 to 5,000 r in forty-five to fifty days rarely have been exceeded in this age group. When the child has been subjected to a craniotomy with some degree of surgical removal of tumor, irradiation may have to be delayed two weeks.

The over-all results of treatment in terms of survival rates, five, ten and fifteen years after treatment in the present group of 79 children, seemed to indicate that the length of survival in this entire age group surpassed that of the total series of 399 cases (*cf.* Table IV and Table XVI). That impression was further supported by the fact that 25 or 31.7 per cent of the children irradiated for various intracranial tumors are still living, five to twenty years afterward. Of those who are now deceased, 5, or another 6.3 per cent, lived more than five years following irradiation, which makes a total of 30, or 38.0 per cent who survived five years or longer after diagnosis and treatment.

TABLE XVI

PRIMARY INTRACRANIAL TUMORS IN CHILDREN AGED FIFTEEN YEARS OR LESS*

Length of Survival	
38.0%	or 30/79 have lived over 5 years
31.0%	or 13/42 have lived over 10 years
38.4%	or 5/13 have lived over 15 years

* Present series: 79 children adequately irradiated, 1939–1953 Follow-up complete, except for 1 medulloblastoma.

Further comparison between the results achieved in the children and those obtained in the older patients strongly suggested that the adults in general have not done as well as the children.

Because we had rather expected the reverse situation, we have explored the possibility that the more favorable survival rates in children might be more apparent than real. One factor causing the difference in the over-all results might be the large proportion of glioblastoma multiforme in the total series (125) when there was only 1 case in the group of 79 children.

Analysis of results tabulated for the children and for the adults separately for each category of tumor shown in Table XVII provides a selective and realistic comparison of survival rates for the two age groups, respectively, with this segregation. Direct comparison of the five, ten and fifteen year survival rates of 135 adults and 71 children in regard to the six categories of intracranial tumors common to the two age groups has substantiated the fact that with some differences for certain tumors, the children have done better than the adults.

For the astrocytomas, the survival rates have been slightly better for children than adults in each of the five, ten and fifteen year categories of survivors.

The same observations apply to the unclassified gliomata, although in this group the percentages of respective five, ten, and fifteen year survivals are somewhat lower than they are in the astrocytomas.

The children with medulloblastoma have also done somewhat better than the adults, but none of them have survived over fifteen years, so far.

Children with mid-brain tumors also have an edge over the adults. Pontine tumors seem to respond better in adults than in children initially, but the ten and fifteen year survival rates are better in children.

Sarcomas, so far, have been more favorable in adults than in children, but none of these patients have lived over fifteen years as yet.

Of the 40 adults and 11 children in this comparative analysis who could have lived over fifteen years, only 4 (10 per cent) of the adults (all astrocytomas) have done so; whereas 3 (27.2 per cent) of the children (1 astrocytoma, 1 glioma unclassified, 1 mid-brain tumor) are living over fifteen years since irradiation.

Further summary of our experience in the irradiation of children aged fifteen or less for primary intracranial tumors is presented in Table XVII. Because the number of cases in each category of tumor is relatively small, no attempt was made to calculate percentage survival.

For the children who are deceased, the average survival in months has been estimated in each category of tumor. This average survival has been the lowest (10.3 months) in the brain stem tumors and in the medulloblastomas (15.3 months). It is nearly thirty-six months or better in sarcomas, mid-brain tumors and astrocytomas.

As for the children who are still living,

TABLE XVII

PRIMARY INTRACRANIAL TUMORS IN CHILDREN AGED FIFTEEN YEARS OR LESS

Summary 1939–1953

	No. of Cases		Average Survival in Months		Longest Survivals in Months
	Deceased	Surviving	Deceased	Surviving	
Astrocytoma	5	7	38.2	111.3	Deceased: 109 Surviving: 72-75-83-96-118-127-208
Glioma Unclassified	5	4	21.4	131.0	Deceased: 48 Surviving: 60-95-156-225
Medulloblastoma	24	4	15.3	102.5	Deceased: 121 Surviving: 74-75-118-143
Mid-Brain Tumors	5	2	37.5*	140.0	Deceased: 74-84 Surviving: 65-216
Brain Stem Tumors	7	2	10.3†	158.0	Deceased: 17 Surviving: 141-175
Sarcoma	5	1	33.6	138.0	Deceased: 52-56 Surviving: 138
All Others	3	5	23.7	114.8	Deceased: 62 Surviving: 61-62-93-152-206

25/79 cases or 31.6 per cent surviving five to twenty years.
5/79 have died five to twenty years after irradiation.

* 43 mo. in adults.
† 38 mo. in adults.

TABLE XVIII

PRIMARY INTRACRANIAL TUMORS IN CHILDREN AGED FIFTEEN YEARS OR LESS*

Quality of Survival	
86.6%	resumed active life
6.7%	had partial disability, but were not incapacitated
6.7%	totally incapable of self care

* Present series: 79 children adequately irradiated, 1939–1953; 30 of 79 children having survived over five years.

the average survival time varies practically from nine to thirteen years in each category of tumor. Five children are alive over fifteen years with survivals ranging from 17.3 to 18.7 years, and they are all well. Seven others are alive between ten and fifteen years after irradiation and 2 more had reached 118 months of good survival by the end of 1958, when the date for this analysis was closed. Another had just died after 120 months of useful survival until the fatal recurrence. Of the 15 patients who are enjoying a long survival, 7 were under ten years of age and 5 aged ten to fifteen years when irradiated, the youngest being one and one-half and three and one-half years old, respectively.

The quality of survival in the 30 of 79 children who have survived over five years after irradiation (Table XVI) has been very good, being slightly better in children than in adults (*cf.* Table III and Table XVIII).

Only 4 of the 30 children who have survived over five years after irradiation are not perfectly well: 1 treated for cerebellar astrocytoma has unsteady gait; 1 with unclassified glioma is slow to learn in school; of 2 who were treated for sarcoma, 1 is mentally slow while the other is blind and hemiparetic.

Not one of these 30 children has shown signs of postirradiation damage to his pituitary gland. Three are now married and have children.

A considerable number were in very poor general and neurologic condition when irradiation was initiated. The majority of these improved dramatically. Only a few had residual disability after completion of treatment, or subsequently, until recurrence or their final episode.

In the general discussion on sarcomas we have reported the only case of postirradiation necrosis of which we know in the total series of 399 primary intracranial tumors which have been irradiated adequately. This was a child re-irradiated for recurrent intracranial sarcoma.

We believe that we are fully justified to conclude that children with malignant intracranial neoplasms can be irradiated adequately and without fear of undue sequelae under the program used for the irradiation of the present series. It is realized that a series of 79 cases is small for strict statistical purposes, but it is probably sufficient to indicate a strong trend in results. It has been very encouraging to find that our experience indicates that children, in general, can be expected to do as well as, and probably better than adults in terms of long and useful survival.

CONCLUSIONS

Our twenty year experience with the irradiation of neoplasms involving the central nervous system is based upon a total series of 826 cases of which 534 patients were adequately treated five to twenty years ago. Analysis of the results can be summarized as follows.

Ionizing radiation therapy can play a major role in the management of: (a) primary intracranial malignant neoplasms; and (b) intracranial metastases from primary malignant neoplasms elsewhere.

Resumption of useful life can be effected in a significantly high proportion of cases.

Prolongation of survival by judicious combination of surgical procedures and irradiation appears to be superior to that obtained by surgery alone.

The beneficial effect of irradiation in the control of tumors of the mid-brain and brain stem (pontine zone) affords major improvement in prognosis for these heretofore virtually hopeless cases.

Properly employed, irradiation does not

create clinically detectable damage to the normal brain and brain stem. Histologic evidence of irradiation damage resulting from such therapy has not been detected in cases subjected to subsequent operation or autopsy.

However, one case showed postirradiation necrosis and that as a sequel to retreatment through portals which were virtually identical to the earlier therapy.

So far, no opacification of the ocular lens has been detected in any case which would be attributable to the radiation therapy employed.

In certain tumors, irradiation should be accorded the major responsibility, surgical intervention being reduced to the minimum required for decompression and identification of tumor type.

Cases of known or suspected primary malignant neoplasms of the mid-brain and especially of the brain stem often have to be treated on the basis of clinical evidence alone, without subjecting the patient to the hazard of any attempt to obtain biopsy identification or confirmation.

Selected patients with known or suspected metastases to the brain or brain stem from malignant neoplasm elsewhere can be enabled to resume and maintain useful life for a significant period of time.

Children with malignant intracranial neoplasm can be treated adequately with irradiation without danger of undue sequelae.

No disturbance of normal growth and development resulting from therapeutic irradiation of the brain or brain stem has been observed in 79 children who were included in the detailed analysis of results of 399 primary intracranial neoplasms which have been adequately irradiated. All had the possibility of living five years or more after treatment.

Although in the majority of those children the pituitary gland could not be protected and has therefore received as much radiation as the primary neoplasm itself, there is no detectable evidence that this gland has been adversely affected in any of the 30 children who have survived five to twenty years.

To achieve adequate irradiation with virtually no postirradiation complication, it is our firm conviction that increased intracranial pressure must be controlled with effectiveness and that irradiation be accomplished in a single protracted course with an optimum dose-time relationship.

In this series the results, assessed in terms of length of survival and quality of survival and also in respect to the type or location of tumor concerned, suggest that, in general, children can be expected to do better than adults.

Department of Radiology
Royal Victoria Hospital
Montreal 2, Quebec, Canada

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TECHNIQUE FOR INTRACAVITARY IRRADIATION OF THE NASOPHARYNX

By HERMAN D. SUIT, M.D.,* RALPH S. LLOYD, D.D.S.,† J. ROBERT ANDREWS, M.D.,* *and* STANLEY E. SNEIDER, M.D.*

BETHESDA, MARYLAND

THE effective treatment of certain tumors of the nasopharynx by ionizing radiations may require the application of a nasopharyngeal source as a supplement to external irradiation. Various techniques for the intracavitary irradiation of the nasopharynx have been described. Some of these are listed in Table I.

We recently had occasion to treat 2 children (five and seven years of age) with rhabdomyosarcoma of the nasopharynx. There were no clinically evident metastases and treatment was to be by irradiation with both external beam and intracavitary sources. In respect to the intracavitary irradiation one of us (R. L.) suggested that an accurate mold of the nasopharynx could be made and the radiation source carried in this mold. Four such molds have been prepared without difficulty.

The advantages of an accurate mold of the nasopharynx to hold the radiation source are several: the precise positioning of the mold permits the fixation of the radiation source either centrally or eccentrically, as required, so as to irradiate mainly the tumor bearing area; the impression of the tumor residue is demonstrable on the mold and the radiation source can be positioned in relation to the tumor by direct inspection; and the technique is simple and surgical defects in the palate or nasal septum are not required for most tumors. The total time required to make the mold is about one hour.

TECHNIQUE

The technical plan is: (1) to prepare an impression of the nasopharynx; (2) to duplicate the impression in acrylic resin plastic; (3) to load the radiation source into the completed mold; and (4) to position the mold in the nasopharynx.

The patient is maintained under orotracheal general anesthesia for a total of sixty to seventy-five minutes. To accomplish the procedure in the minimum time, the dental technician arranges in his laboratory all

TABLE I

SOME REPORTED TECHNIQUES FOR INTRACAVITARY IRRADIATION OF THE NASOPHARYNX

Method	Surgery Required	Author
Metal applicator introduced through oropharynx	None	Blady, 1938[1]
Sponge rubber cork with central radium source	None	Cade, 1948[3] Paterson, 1949[4]
Central Co^{60} source fixed to applicator placed in nasopharynx through palatal fenestration	Resection of palate	Windeyer and Wilson, 1955[7]
Packing nasopharynx with radium containing bakelite applicator	None	Van Herick and Erich, 1955[6]
Central Co^{60} source in Foley catheter	Resection of nasal septum	Sooy, F., 1956[5]

* Radiation Branch, National Cancer Institute, National Institutes of Health, Public Health Service, Department of Health, Education, and Welfare, Bethesda, Maryland.

† Dental Department, Clinical Center, National Institutes of Health, Public Health Service, Department of Health, Education, and Welfare, Bethesda, Maryland.

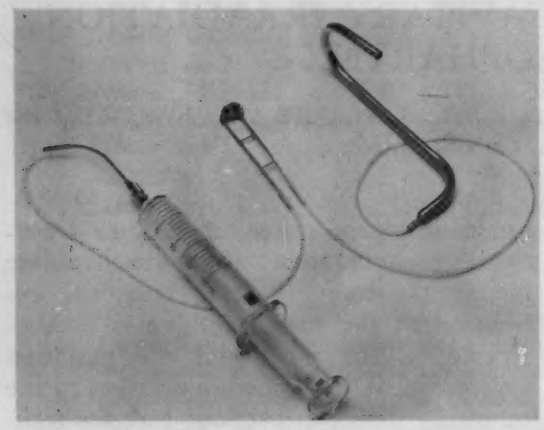

FIG. 1. Photograph of the carrying and cooling tray for the impression compound. Rapid cooling is effected by forcing ice water through the tubing, which is an integral part of the tray.

the tools and compounds required in the preparation of acrylic molds. When he is ready to receive the impression the anesthesia is begun.

An appropriate mass of black dental impression compound is attached firmly to the carrying and cooling tray (Fig. 1). The compound is carried on the tray and forced into the nasopharynx by digital pressure (Fig. 2). The special cooling tray is used to carry the impression material and by circulating ice water through the tray the compound can be hardened within four minutes. To facilitate removal of the mold, care should be taken to prevent the compound from projecting into the oropharynx.

A dental technician receives the impression and duplicates it in Durabase, a quick-cure pink acrylic, by the ordinary split mold technique. Two ties are attached to the mold at points corresponding to the posterior choanae and to the oropharyngeal surface. These are attached by introducing a knotted tie into a hole drilled in the mold and then securing the tie with a thin mix of quick-cure acrylic.

The mold gives a rather accurate picture of the extent of the nasopharyngeal tumor mass so that the position of the source or sources which will provide the optimum irradiation of the mass can be determined. Direct measurements of the source-surface distance are made to the various points of treatment interest. The sources are then positioned in holes drilled in appropriate sites of the mold. Finally, the mold is placed in the nasopharynx and fixed by the ties. A sketch of the mold as prepared and used in the case of a five year old girl is shown in Figure 3.

This five year old girl presented with a rhabdomyosarcoma of the nasopharynx. A tumor exposure dose of 5,000 r had been delivered to the nasopharynx and surrounding tissue, including a small segment of the midbrain, by 2 mev. roentgen rays. A small nasopharyngeal mass persisted and the mold shown in Figure 3 was prepared. By means of radium fixed within the mold, an additional exposure dose of 3,000 r was delivered in two sessions at an interval of ten days, this dose being computed for a 1 mm. depth in tissue. By appropriate fixation of the radium source in the mold, the exposure dose of 3,000 r was concentrated to the region of the lesion on the right side of the

FIG. 2. Application of carrying and cooling tray and the impression compound into the nasopharynx.

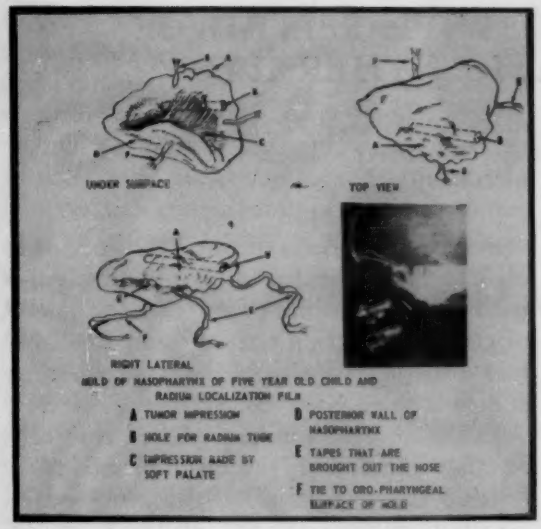
UNDER SURFACE
TOP VIEW
RIGHT LATERAL
MOLD OF NASOPHARYNX OF FIVE YEAR OLD CHILD AND RADIUM LOCALIZATION FILM
A TUMOR IMPRESSION
B HOLE FOR RADIUM TUBE
C IMPRESSION MADE BY SOFT PALATE
D POSTERIOR WALL OF NASOPHARYNX
E TAPES THAT ARE BROUGHT OUT THE NOSE
F TIE TO ORO-PHARYNGEAL SURFACE OF MOLD

Fig. 3. Drawings of a mold, and its ties, used for nasopharyngeal irradiation with a roentgenogram showing localization of radium carried in a nasopharyngeal mold.

nasopharynx and a calculated exposure dose of only 400 r reached the left nasopharynx and the nearest portion of the midbrain. The radium localization roentgenogram is shown in Figure 3.

SUMMARY

A technique for the preparation of accurate plastic molds of the nasopharynx has been described. These molds are used as radiation source carriers in the supplementary irradiation of certain neoplasms of the nasopharynx. No surgical resection of the palate or nasal septum is required to obtain accurate positioning of the mold and radiation sources.

J. Robert Andrews, M.D.
Radiation Branch, National Cancer Institute
Public Health Service
Department of Health, Education, and Welfare
Bethesda 14, Maryland

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INITIAL EXPERIENCE WITH SPLIT-DOSE PERIODIC RADIATION THERAPY*

By PAUL W. SCANLON, M.D., *Section of Therapeutic Radiology*
Mayo Clinic and Mayo Foundation†
ROCHESTER, MINNESOTA

THE resurgence of interest in radiobiology within the past several years, together with the ever-broadening scope of basic radiobiologic knowledge, often occasions reappraisal of some of the fundamentals we have all more or less taken for granted. One of the fundamentals I should like to re-evaluate in this paper is the accepted validity of continuous unbroken daily radiation therapy as advocated by Coutard in the 1930's and carried on more or less empirically ever since.

ANTECEDENT WORK

During the past several years the author has evolved a system of discontinuous radiation therapy in which irregularly spaced series of treatments are separated by intervals of rest which presumably permit mitotic and metabolic recovery. This recovery period, theoretically at least, allows restoration of radiosensitive elements, a process which is not possible under the impact of continuous radiation therapy. This departure from conventional techniques of fractionated dosage was based on the results of earlier investigations by British radiobiologists of a decade or more ago, plus the author's[19] experience with the apparently superior end results of accidentally and unplanned interrupted radiation therapy. The prognostically unfavorable group of 25 far-advanced malignant lesions of the head and neck included in this paper represents the author's initial experience in purposely departing from accepted radiation therapy disciplines. The results of this clinical experiment are presented not so much in an attempt to demonstrate some degree of apparently increased effectiveness of these methods as to elaborate on the author's changing views with regard to some of the basic problems of clinical radiation therapy and to stimulate others, if possible, to make similar clinical trials.

It would seem well established that cells in the immediate premitotic and early mitotic phase constitute the most radiosensitive element of any given cell population, benign or malignant, and that depopulation of this element can be effected by means of relatively small amounts of irradiation.

The exact percentages probably are unimportant, but it has been estimated that cells in or near this sensitive phase constitute 2 to 15 per cent of the total cell population of any given tumor, and that it is quite possible to eradicate this element with as little as 300 to 400 r. It has been assumed, erroneously I believe, that, once this radiosensitive element has been eliminated by the initial few hundred roentgens, continued mitotic activity will day by day replenish a small fraction of these radiosensitive cells, thus affording a continuum of cells susceptible to the effects of additional irradiation. A review of the pertinent radiobiologic literature will convince the reader that such is not the case; rather, that under the stress of a noxious or potentially harmful environment—in this case irradiation—normal mitotic and metabolic activity is interrupted and mitosis is held in abeyance. This is a truism applicable to all of nature: reproduction will not take place or is accomplished only with great difficulty in the face of external stress. If this be the case, then continued

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† The Mayo Foundation, Rochester, Minnesota, is a part of the Graduate School of the University of Minnesota.

therapy after the first few days is concerned only with adult or resting malignant cells, not particularly more radioresponsive than the adult resting cells of surrounding normal tissue. The author does not wish to ignore the very significant tumor-bed effect which comes into play when a tumor dose of approximately 1,500 to 2,000 r is reached,[11] but for the purposes of this paper will bypass this most important effect for the moment.

Probably equally important, mitotic activity is held in abeyance as long as the external stress of radiation therapy is operative. If this be true, it is conceivable that continuous daily irradiation, once the radiosensitive mitotic and premitotic elements have been depleted, with nothing but relatively radioresistant adult cells to act upon, is not only wasteful and unproductive, short of near-cautery doses, but that by keeping mitotic activity in abeyance during further irradiation actually is detrimental to the continued effectiveness of therapy.

It is logical, therefore, to inquire what might happen if, after the initial phase of cellular destruction, therapy is suspended long enough to allow tissue recovery and resumption of mitotic activity, thus enabling restoration of the radiosensitive elements of a tumor. Space does not permit a repetition of previously published arguments along these lines.[19] Suffice it to say that Spear and Glücksmann[20,21] have shown that once maximal cellulolethal effect has been achieved with the initial irradiation, when therapy is then suspended there is a gradual return of mitotic activity, dependent on several variable factors to be discussed later, not only to preirradiation levels but indeed sometimes in excess of these levels in an overcompensating manner. Whether this is a true overcompensation phenomenon or merely an additive effect from cells simply delayed in their mitotic cycle during the period of suppression added to others in their normal reproductive cycle is not known. However, whatever the reason, the presence of greatly increased mitotic figures at this particular moment is indicative of increased radiosensitivity. Coutard,[4] Koller and Smithers,[12] Sambrook *et al.*,[18] the author,[19] and undoubtedly others by means of interrupted radiation therapy of various types have attempted to capitalize on this "golden moment" of increased radiosensitivity to increase the cellulolethal effect of their therapy. That this ebb and flow of mitotic activity under the impact of irradiation is more than theory is well borne out, I think, by the very careful works of Canti and Spear,[1] Spear and Glücksmann,[20,21] Koller,[10,12] Lasnitzki,[13,14,15] Glücksmann,[5] and others. It is in the timing of this renewed sensitivity or return of mitotic activity that the transition from theory to actual practice becomes most tenuous, and it is here that the need for additional investigation is most pressing.

It seems fairly certain that the degree and duration of mitotic suppression and the extent of recovery will depend on many factors: the size of the initial dose and the sum total of its biologic effect, the type of tissue and its relative activity at the time of irradiation, the condition of the tumor bed and related factors such as the presence of infection, the vascularity of the tumor bed and the resulting oxygen saturation of the tissues in question, anemia, the presence of cytotoxins and probably a host of other variable influences not the least important of which is the general nutrition of the organism concerned and the status of endocrine balances. Presented with this seemingly infinite number of variables, it would seem almost impossible arbitrarily to select the optimal hour or day of maximal mitotic recovery. It may well be, however, that this factor of time is not quite so critical as first imagined. True enough, if after the initial delay or period of recovery the second series is started before peak mitotic activity is attained there may not be as great a cellulolethal effect as would be obtained if therapy were delayed still longer. On the other hand, if the second series is delayed too long, the overcompen-

sating increased mitotic activity may have returned to pre-irradiation levels. In either case, although the effect would not be as maximal as that which follows irradiation timed to coincide with the peak of mitotic recovery, the cellulolethal effect would still be far greater than that obtained from continuous uninterrupted irradiation in which mitotic activity had been abolished early and which remains at negligible levels under the influence of continuing therapy.

It was on this premise that an experimental type of broken-dose or periodic radiation therapy was initiated in the 25 cases of advanced malignant processes of the head and neck presented herein. Previously published work of the author,[19] concerned with the results of unplanned, irregularly interrupted radiation therapy which chanced to be carried out thus for a number of reasons, revealed an apparently increased degree of effectiveness which was difficult to explain on the basis of ordinary radiation therapy principles. A time analysis of 88 cases of treated nasopharyngeal malignant lesions, 43 cases of epithelioma of the anus and 46 cases of malignant processes of the palatine tonsil revealed that when such broken-dose therapy was employed the five year survival rates were three to four times as great as those obtained from conventional uninterrupted radiation therapy. These better results apparently were not influenced by any preferential staging, by distribution of prognostically more favorable pathologic subgroups or by preferential dosage received. The only apparently evident factor which did vary between the two groups of patients was the continuity of daily treatments, and it is to the discontinuity of such therapy that the author attributes the better results obtained when the broken-dose technique was used. With these results in mind, and to gain additional support for the author's views on the merit of interrupted discontinuous radiation therapy, the following clinical experiment in broken-dose therapy was devised with purposeful and planned interruptions in the continuity of daily treatments.

NATURE OF THE PRESENT STUDY

Twenty-five patients with far-advanced malignant neoplasms of the head and neck were treated periodically by the author through March, 1958. The study includes all lesions treated periodically with the exception of one which affected a patient who died shortly after radiation therapy was begun. Although other malignant processes of the thorax and abdomen were treated during the same time interval with the broken-dose system, the author chose, because of the difficulties in determining the response of the tumors in these cases, to limit this initial review to lesions of the head and neck in which the ease and certainty of follow-up examinations enhance accuracy in assessing the response to treatment.

In discussing different types of malignant lesions of the head and neck as a composite group, only the most general sort of staging is possible. For purposes of this review three stages were selected.

Lesions still confined to the site of origin and not more than 2.5 cm. in diameter were classed as Stage 1.

Lesions larger than 2.5 cm., and those which had extended beyond the site of origin or into adjacent neighboring soft parts, were classed as Stage 2.

Those lesions which had metastasized to regional lymph nodes or those which had involved neighboring bone or nerve tissue by invasion were classed as Stage 3.

In the 25 cases reviewed herein 22 lesions were Stage 3 and the remaining 3 were Stage 2. There were no early favorable Stage 1 lesions in this series, a factor which should be given considerable weight in evaluation of the results obtained. All malignant lesions were verified histologically, a specimen being taken for biopsy from the primary lesion except as otherwise stated.

THE TIME FACTOR

In a discussion of split-dose therapy it may be well to employ a numerical abbreviation to denote days under active

treatment spaced in such a way that the interval days of rest appear as superscripts above the days of active treatment. Hence the ideal split-dose scheme would be represented as $3\ ^{7}\ 6\ ^{21}\ 14 = 6{,}000$ r tumor dose (TD) or whatever total dose is desired. This of course would mean an initial three days of therapy followed by seven days' respite, another six days of therapy followed by a three week respite, and then another fourteen days or more of therapy in which the prescribed dose is carried to completion, usually in increments of 300 r (air). The ideal split-dose scheme alluded to here represents the author's current concept of the best possible periodic radiation therapy, based on experience in the periodic management of more than 65 patients treated subsequent to March, 1957. The time intervals employed in most of the initial 25 cases reported herein vary somewhat from this "ideal scheme" and represent the author's initial exploratory attempts at finding a workable solution to the extremely complex problem of split-dose radiation therapy.

Selection of the time interval of necessity was empiric. The first interval of seven days was based on the results of previous radiobiologic investigation which revealed a return of mitotic activity in tissue cultures and animal tissues within seven to ten days after an initial dose of 300 to 1,000 r (Glücksmann[5] and Lasnitzki[13]). A later work of Koller[10] revealed that when squamous cell epithelioma was irradiated with a single dose of 300 r and no additional irradiation was given in the interim, the dividing cells of the tumor were completely free of chromosomal injuries seventy-two hours after the initial dose. This result probably would indicate, from a morphologic standpoint at least, that the damaging effect of the initial 300 r would have been dissipated within three days. Furthermore, in the analysis of 3 cases in which squamous cell epithelioma was subjected to single doses of 2,800 to 3,000 r, with the effects judged by means of serial biopsy, the number of cells with chromosomal injuries was found to be highest on the eighth post-treatment day, decreasing very rapidly thereafter. On the other hand, Koller and Smithers[12] found that in a few instances mitotic activity might be suppressed for up to forty-five days after an initial dose of 300 to 400 r. It would seem, therefore, that the recovery time is a very variable phenomenon probably influenced by a host of other factors as mentioned earlier herein. The initial seven days of rest obviously is only an approximation, and until some practical clinical or laboratory test is forthcoming which will indicate the optimal recovery time, periodic radiation therapy must of necessity rest on rather empiric foundations.

The second interval of three weeks' rest in the split-dose scheme under description was chosen on an even more tenuous basis. It does, however, constitute a major difference in this periodically treated series as opposed to other series reported earlier. It is my feeling that mitotic and metabolic recovery times will lengthen progressively as more and more irradiation is given. It cannot be expected that a tissue will always recover from a second dose of irradiation with the same readiness with which it recovered from the first such dose. With this in mind, the second rest interval was selected which trebled the recovery time of the initial series and at the same time more closely approximated the monthly intervals of the old once-favored erythema-dose technique of roentgen therapy.

I think this failure to allow for progressively longer recovery times as therapy progressed was a major shortcoming of the earlier reported schemes of periodic irradiation. Coutard,[3,4] for instance, recommended the following split-dose patterns: (1) for highly undifferentiated carcinoma, $6\ ^{14}\ 6 = 6{,}000$–$7{,}000$ r; (2) for moderately differentiated carcinoma, $3\ ^{7}\ 3\ ^{10}\ 3 = 7{,}200$ r; (3) for well-differentiated carcinoma, $2\ ^{9}\ 2\ ^{11}\ 2\ ^{11}\ 2 = 7{,}600$–$8{,}000$ r.

Sambrook and associates,[18] treating

squamous cell epitheliomas, basal cell epitheliomas and recurrent cutaneous adenocarcinoma of the breast, employed two different split-dose schemes: I $\frac{7}{}$ I $\frac{7}{}$ I $\frac{7}{}$ I $\frac{7}{}$ I = curative dose levels of varying amounts, and the more satisfactory and less severe I $\frac{3}{}$ I $\frac{4}{}$ I $\frac{3}{}$ I $\frac{4}{}$ I $\frac{3}{}$ I, and so on, carried to comparable dose levels. The latter scheme constituted in essence 500 r repeated twice weekly to whatever dose level was thought desirable. Apparently neither of these two dosage schemes took into account the progressively lengthening recovery times as therapy progressed.

The interesting experiment of Koller and Smithers[12] was much more like the author's present scheme, but varied from case to case, so much depending on the cytologic analysis of the tumor response as charted by serial biopsy that no general formula can be given.

Although he failed to take into account progressively longer recovery times as therapy progressed, Coutard recognized that recovery times probably differ for varying tissues and varying tumors. If and when the validity of periodic radiation therapy is ever established, investigation will almost certainly reveal that such treatment of an adenocarcinoma will require a split-dose scheme quite different from that required of a squamous cell carcinoma. For the present, however, with so many other variables operative, the author does not feel justified in attempting to speculate on the subtle differences between the various pathologic subgroups encountered in this series of 25 malignant lesions of the head and neck.

There were many instances in which the author of necessity deviated from the preferred three-series treatment plan. This usually meant employment of a two-series scheme such as 12 $\frac{21}{}$ 12 = curative TD, used mainly for a patient who lived more than 200 to 300 miles from the clinic, for whom it was not economically feasible to return more than once in a short period. The variation also was resorted to when advanced age or general debility of a seriously ill patient precluded more than a minimal number of visits to the clinic.

The cases are presented in abridged form in Tables I and II.

COMMENT

In any discussion of a new approach to therapy or change in conventional techniques, the question of the relative effectiveness of the change is of paramount importance, and rightly so. However, the results of cancer therapy by general agreement usually are assessed in terms of five year survival rates. Since the period required for collection of enough cases for reporting is two or three years and since the period required for observation is five years, a lapse of from seven to eight years from the inception of an idea to its presentation therefore is almost inevitable. This time lag is all the more serious when it is considered that the death rate from cancer is some 250,000 cases a year.

The cases I have presented are reported not so much in an attempt to prove the merit of this particular system of broken-dose or periodic radiation therapy—obviously impossible in the face of follow-up studies involving only one year to three years—but to stimulate similar clinical trials by others. Thus, by a pooling of experience the time lag of seven to eight years mentioned above may be obviated. Probably more important, it may be that other patterns of broken-dose therapy will be discovered which potentially are more effective than those I have outlined.

The preliminary results reported herein of course are not conclusive. They are, however, suggestive of a degree of increased effectiveness over conventional radiation therapy techniques sufficient to warrant additional investigation by others. When an attempt is made to assess these preliminary results, I think it is most important to bear in mind the fact that the le-

sions in these cases were much advanced, 22 of the 25 being of a stage at which one commonly expects a five year salvage rate of from 10 to 15 per cent. Many patients had undergone radiation therapy previously (Cases 2, 14, 15, 18, 21, 22 and 25) and prior attempts at radical surgical treatment (Cases 8, 14, 15, 24 and 25). The lesions of some were so very far advanced clinically as to be considered hopeless from every conceivable aspect (Cases 15, 21, 22 and 25). Only the remote possibility of benefit from therapy could justify inclusion of such patients in a series in which curative therapy was attempted.

On the basis of Stages 1 through 3, 22 of these patients had lesions which were Stage 3, and 3 had lesions of Stage 2. No patients who had favorable Stage 1 lesions were included. At the time of this writing, after periods of observation of from one year to three years, apparent eradication of all foci of malignancy within the fields treated had been achieved in 13 of the 25 cases. In one of these 13 cases a lymph node outside the field of irradiation became metastatically involved. This node was excised. In another case an undiagnosed pulmonary lesion developed, the causation of which was not entirely clear and which subsequently was controlled with radiation therapy. Thus, the author considers that the objective of therapy, meaning eradication of all disease within the fields of treatment, was achieved in 13 of the 25 cases.

I shall make no attempt to compare this one to three year arrest rate of 50 per cent with the usual five year survival rate of 5 to 15 per cent ordinarily encountered in Stage 3 malignant lesions of the head and neck. However, it may be pointed out that McGrath and Schmidt,[16] in a study of 117 patients with epidermoid carcinoma of the oral cavity, noted that a charting of all recurrences showed that 84 per cent appeared within the first twelve months and that 98 per cent appeared within two years after treatment. It was their belief that a follow-up study of two years in oral cancer is as significant as one of five years. If this be true, it may be that the one to three year arrest rates reported herein are more significant than first presumed. It is also quite logical to point out that given a more nearly representative series of malignant lesions of the head and neck, including a normal sampling of Stage 1 and 2 lesions, and particularly given a series which has not been so heavily overloaded with previously treated patients, considerably better results from periodic therapy might have been attained.

If all patients previously treated either radiologically or surgically are excluded, there remain 15 who had malignant lesions not previously "interfered with." Of these 15 patients 11 (73 per cent) were free of disease for a year to three years after periodic therapy, a result appreciably better than the author would have expected among patients with predominantly Stage 3 lesions after conventional continuous radiation therapy.

Furthermore, in the 12 cases in which irradiation was a "failure," 4 patients obtained what can be considered excellent palliative results. In Case 17, a hopelessly inoperable carcinoma of the maxillary antrum had extended outside the antrum in almost every direction. This massive lesion was "converted" into an operable lesion by broken-dose therapy and the patient remained well and free of disease after surgical maxillectomy for approximately a year. In 3 other cases the primary treated malignant process remained under good control: one patient (Case 18) was living with residual cancer and the others (Cases 21 and 23) had died of disseminated malignant disease, at the time of this report.

If these results do not prove a superior degree of effectiveness of broken-dose or periodic therapy, they at least suggest such superiority. I believe even the most skeptical would admit that the broken-dose technique probably is no less effective than conventional radiation therapy.

There remains, however, another major advantage of such therapy, and that is the ease with which patients tolerate it. This

desirable feature, coupled with the effectiveness of the method, makes it a particularly attractive change from conventional techniques.

It was with gratification that the author noted, in the early stages of this study of periodic therapy, not only encouraging early responses of the tumors but also definitely less severe immediate postradiation reactions and an apparently greater toler-

TABLE I

ESSENTIAL CLINICOPATHOLOGIC DATA: 25 PATIENTS WITH MALIGNANT LESIONS OF THE HEAD AND NECK TREATED BY SPLIT-DOSE PERIODIC RADIATION

Patient	Age, Sex	Location, Stage	Extension of Primary Lesion	Metastatic Lymph Nodes, Size and Number	Lesion, Grade
1	67 M	Tonsil, pharynx, Stage 3	Nasopharynx, anterior and posterior pillars, lateral hypopharyngeal wall, piriform sinus, epiglottis	Yes—2 cm. several	Squamous cell epithelioma, 4
2	36 F	Parotid, Stage 3	8 cm. mass from mastoid to anterior ramus of mandible. Paresis CN v and vii	Submaxillary gland	Cylindroma
3	67 M	Base of tongue, Stage 3	2 by 3 cm. nonulcerated carcinoma of base	Yes—3 cm. several	Squamous cell epithelioma, 4
4	39 M	Nasopharynx, Stage 3	Entire nasopharynx filled	Yes—3 cm. single	Lympho-epithelioma
5	52 M	Floor of mouth, Stage 2	From canine area to opposite molar, involvement of gingival ridge	No	Squamous cell epithelioma, 3
		(New superficial lesion outside treatment field, 2 yr. later)			Squamous cell epithelioma, 2
6	35 M	Nasopharynx, Stage 3	Nasopharynx, vault	Yes—5 cm. several	Undifferentiated Grade 4 cancer
7	74 M	Tongue, tonsil, Stage 3	4 cm. mass involving tonsil, adjacent base of tongue	Yes—3 cm. single	Squamous cell epithelioma, 2
8	63 F	Parotid, Stage 2	4 by 3 by 3 cm. mass over ramus of mandible, 3 by 2 by 2 cm. mass deep to mandible	No	Adenocarcinoma, 2
9	53 F	Parotid, Stage 3	6 cm. mass in parotid, with paresis of CN vii	No	Cylindroma
10	58 F	Antrum, Stage 3	Previous radical maxillectomy with residual carcinoma in pterygoid fossa, temporal muscle	No	Squamous cell epithelioma, 4
11	75 M	Base of tongue, Stage 3	Entire hypopharyngeal aperture filled with bulky neoplasm	Yes—8 cm. single	Squamous cell epithelioma, 3
12	88 M	Tonsil, Stage 3	Entire fauces, hard and soft palate, adjacent base of tongue	Yes—2 cm. single	Squamous cell epithelioma, 4
13	64 M	Larynx, Stage 3	Primary true cord, multiple metastatic lymph nodes removed by block dissection prior to Co^{60} treatment	Yes several	Squamous cell epithelioma, 3
14	53 M	Base of tongue, hypopharynx, later clavicular metastasis, Stage 3	5 cm. ulcerating primary, base of tongue with extension down lateral hypophyseal wall into pyriform sinus	Yes—7 cm. single	Squamous cell epithelioma, 3
15	57 M	Scalp, Stage 3	10 by 12 cm. defect in left parietal scalp rimmed with active carcinoma, calvarium exposed	Yes—1–2 cm. several	Squamous cell epithelioma, 2
16	49 M	Posterior pharyngeal wall, Stage 2	2.5 by 5 cm. ulcerating carcinoma posterior pharyngeal wall	No	Squamous cell epithelioma, 3
17	71 F	Antrum, Stage 3	Massive antral malignant lesion with invasion orbit, cheek, nares, mouth. Extensive osseous destruction	No	Squamous cell epithelioma, 3
18	81 M	Skin, Stage 3	Previously irradiated primary on cheek under control	Yes—4 cm. several	Squamous cell epithelioma, 2
19	78 M	Tonsil, hypopharynx, Stage 3	6 cm. ulcerative carcinoma fauces, lateral hypopharyngeal wall	Yes—4 cm. several	Squamous cell epithelioma, 3
20	68 M	Antrum, Stage 3	Massive antral malignant lesion with invasion mouth and cheek. Osseous destruction gingival ridge	No	Squamous cell epithelioma, 2
21	63 M	Tongue, floor of mouth, Stage 3	Massive ulcerative carcinoma anterior floor of mouth with involvement anterior half of tongue	Yes—8 cm. submental mass	Squamous cell epithelioma, 2
22	70 F	Antrum, Stage 3	Massive antral malignant lesion with invasion mouth and cheek. Osseous destruction anterior antral wall	Yes—2 cm. several	Transitional cell epithelioma, 4
23	61 F	Nose, sinuses, Stage 3	Surgical removal melanoma frontal sinus; involved calvarium left intact	No	Melanosarcoma
24	37 F	Floor of mouth, Stage 3	5 by 2 cm. ulcerative malignant lesion floor of mouth, submental region	Yes—3 cm. several	Squamous cell epithelioma, 2
25	66 M	Palate, Stage 3	5 by 3 cm. mass arising lateral pharyngeal wall, extension along floor of skull	No	Squamous cell epithelioma, 2

TABLE II

ESSENTIAL THERAPEUTIC DATA: 25 PATIENTS WITH MALIGNANT LESIONS OF THE HEAD AND NECK TREATED BY SPLIT-DOSE PERIODIC RADIATION

Patient	Prior Irradition	Prior Surgery	Periodic Co^{60} Treatment,* Tumor Dose	Field Size, Dose Administered	Primary (1) and Secondary (2) Regression
1	o	o	$6 \xrightarrow{20} 8 \xrightarrow{19} 9$† = 5,800 r TD	Bilateral 13 by 14 cm. ports; 5,530 r left, 2,740 r right	Both 1½ yr.
2	Yes	o	$3 \xrightarrow{6} 7 \xrightarrow{12} 14$ = 5,750 r TD	Single 10 by 16 cm. port, 6,850 r	Both 2 yr. Limited radiation myelitis
3	o	o	$4 \xrightarrow{11} 6 \xrightarrow{16} 11$ = 5,000 r TD 3 mo. later, 750 r	Bilateral 8 by 12 cm. ports; 4,500 r right, 2,260 r left	Both 1½ yr. Subsequent squamous cell node removed surgically outside treatment field
4	o	o	$2 \xrightarrow{3} 6 \xrightarrow{23} 15$ = 5,100 r TD	Bilateral 9.5 by 16 cm. ports; 3,750 r right, 3,540 r left	Both 1½ yr.
5	o	o	$3 \xrightarrow{5} 7 \xrightarrow{14} 13$ = 6,250 r TD	Bilateral 7 by 9 cm. ports; 4,140 r to each	Primary 2 yr.
			$5 \xrightarrow{24} 8$ = 4,150 r	Intraoral cone treatment (140 kv. peak); 4,150 r	Primary 1 yr.
6	o	o	$13 \xrightarrow{19} 12$ = 5,000 r TD 3 mo. later, 700 r	Bilateral 10 by 20 cm. ports; 3,500 r to each	Both 1½ yr. Subsequent undiagnosed chest lesion with osteoarthropathy
7	o	o	$3 \xrightarrow{7} 6 \xrightarrow{12} 12$ = 4,900 r TD 3 mo. later, 700 r	Single 9 by 12 cm. port; 6,200 r	Both 1 yr.
8	o	Yes	$13 \xrightarrow{33} 10$ = 5,300 r TD Radon seeds = 5,100 r	Single 8 by 12 cm. port; 6,000 r	Primary 1½ yr.
9	o	o	$14 \xrightarrow{20} 11$ = 6,600 r TD	Single 7 by 11 cm. port; 7,500 r	Primary 1½ yr.
10	o	o	$5 \xrightarrow{6} 24$ = 4,000 r TD Radium needles = 4,000 r	Single 6 by 9 cm. port; 6,000 r	Both 3 yr.
11	o	o	$4 \xrightarrow{10} 12 \xrightarrow{12} 12$ = 6,100 r TD Radon seeds = 4,000 r (primary only)	Bilateral 8 by 9 cm. ports; 3,900 r to each	Both 1¾ yr.
12	o	o	$10 \xrightarrow{24} 10$ = 5,050 r TD	Single 10 by 12 cm. port; 6,000 r	Both 1 yr.
13	o	o	$11 \xrightarrow{13} 12$ = 5,710 r TD	4,750 r to a 10 by 14 cm. lateral port; 2,000 r to a 6 by 6 cm. opposite port	Both 1 yr.
14	Yes	Yes	$12 \xrightarrow{21} 12$ = 5,660 r TD Treatment of clavicular metastasis $8 \xrightarrow{23} 10$ = 5,000 r	Bilateral 10.5 by 13 cm. ports; 5,200 r left, 2,125 r right	(1) Temporary. (2) Yes. Died 1 yr.
15	Yes	Yes	$4 \xrightarrow{9} 6 \xrightarrow{12} 6$ = 3,450 r TD 6 mo. later $4 \xrightarrow{9} 6 \xrightarrow{16} 6$ = 3,400 r TD Both orthovoltage therapy	Irregular fields to conform to cutaneous lesions	Neither responded. Died 1½ yr.
16	o	o	$12 \xrightarrow{22} 12$ = 6,000 r TD 4 mo. later $3 \xrightarrow{9} 6 \xrightarrow{23} 9$ = 5,200 r TD	Bilateral 9 by 10 cm. ports; 4,000 r to each Bilateral 9 by 10 cm. ports; 3,460 r to each	(1) No regression. Died 10 mo.
17	o	o	$11 \xrightarrow{15} 14$ = 5,250 r TD. Recurrence in 7 mo. Surgical maxillectomy.	Single 7 by 10 cm. port; 7,000 r	(1) Temporary. Alive 1 yr. after surgery
18	Yes	o	$4 \xrightarrow{9} 6 \xrightarrow{17} 9$ = 5,200 r TD	Single 10 by 12 cm. port; 5,800 r	(2) Yes. Alive with recurrence 1½ yr.
19	o	o	$3 \xrightarrow{7} 6 \xrightarrow{16} 14$ = 5,500 r TD	Single 9 by 15 cm. port; 7,000 r	Both temporary. Died 10 mo.
20	o	o	$3 \xrightarrow{10} 6 \xrightarrow{16} 12$ = 6,600 r TD	Single 8 by 9 cm. port; 7,250 r	Both temporary. Died 1½ yr.
21	Yes	o	$4 \xrightarrow{11} 6 \xrightarrow{17} 6$ = 4,180 r TD	Single 10 by 10 cm. port; 4,600 r. Orthovoltage treatment	Both temporary. Died 6 mo. with pulmonary metastasis
22	Yes	o	$3 \xrightarrow{10} 6 \xrightarrow{12} 9$ = 4,000 r TD	Single 9 by 9.5 cm. port; 5,400 r	No follow-up. Died 6 mo.
23	o	Yes	$12 \xrightarrow{18} 12$ = 5,900 r TD	Single 8 by 10 cm. port; 6,700 r	Died 6 mo. with pulmonary metastasis
24	o	Yes	$13 \xrightarrow{23} 12$ = 5,950 r TD	Bilateral 11 by 11 cm. ports; 3,800 r right, 3,520 r left	Immediate dissemination outside treatment fields. Died 6 mo.
25	Yes	Yes	$10 \xrightarrow{20} 10$ = 5,200 r TD	Single 9 by 13 cm. port; 6,000 r	No response. Died 5 mo.

* Except for Patients 15 and 21, for whom orthovoltage therapy was employed.

† The abbreviated formula indicates: 6 days treatment, 20 days respite, 8 days treatment, 19 days respite, 9 days treatment = delivering a total tumor dose of 5,800 r.

ance of the patient to high doses. The technique of periodic therapy now employed by the author usually belongs to one of two broad categories: (1) the preferred $3 \frac{7}{} 6 \frac{21}{} 14$ = prescribed tumor dose, employed when the patient lived within a radius of 200 to 300 miles from the clinic and could travel to and from the clinic without too much financial or physical hardship; and (2) the $12 \frac{21}{} 12$ technique, which usually is carried out for patients living at a greater distance from the clinic, particularly if advanced age or poor general condition precluded more frequent visits. Theoretically, at least, the second plan should have proved less desirable, but in actual practice it seemed fully as effective as the first plan.

As a rule, at the end of the second period in the first plan, or at the end of the first period in the second plan (in both instances about the twelfth to fourteenth day after therapy is initiated, when the typical radiomucositis first makes an appearance), therapy is discontinued and the patient is sent home for approximately three weeks or occasionally a month. The radiomucositis at this stage is mild and troublesome usually only for three to five days after therapy has been discontinued. By the time the patient returns for the final series of treatments, the radiomucositis has disappeared and the patient generally feels as well as he did prior to the onset of therapy. I have been continually impressed by the degree of regression of the tumor at this point. In many cases complete disappearance of the lesion has been noted at this stage, where less than half of the prescribed dose has been delivered. In many other cases regression of the tumor, although not complete, was very considerable.

During the later stages of the last series of treatment, radiomucositis for the second time becomes a problem. At such a time the reaction is somewhat more severe than the initial radiomucositis, but it is still very much less than that which follows conventional radiation therapy. Most patients are able to eat fairly comfortably within a week to ten days, and in many cases within even a shorter time than this. The general reactions of fatigue, malaise and toxicity appear to be less marked and severe when the split-dose technique is used and constitute one of the outstanding advantages of this type of therapy, particularly for the aged and debilitated patient, or the one with advanced cardiac or pulmonary disease.

By way of illustration, Case 18, an eighty-one year old man with a metastatic epithelioma in the upper part of the neck, received 5,800 r to a 10 by 12 cm. lateral portal in the neck for an estimated tumor dose of 5,200 r at a depth of 3 cm. This man was in exceedingly poor general condition. He was blind and so infirm that he had to be lifted from his wheel chair to the treatment table, yet he withstood this therapy with very little difficulty. He had only a suggestion of mild soreness of the throat after therapy and the soreness cleared satisfactorily within a week to ten days.

Seven of the 25 patients reported upon herein were in the eighth decade of life or more, the oldest being eighty-eight years old. They withstood with comparative ease high doses of curative therapy which might have been exceedingly difficult if conventional techniques of therapy had been employed. This single factor of enhanced tolerance has been so striking that what originated as an experimental technique now has become almost a routine and preferred management of all patients with Stage 2 and Stage 3 malignant lesions of the head and neck treated by the author, wherever possible. Even if the question of therapeutic effectiveness could be excluded, it is the author's conviction that any modification of existing methods which would serve to attenuate and minimize the irradiation morbidity which all too often follows high-dose curative techniques is worthy of serious consideration and further clinical trial.

In addition to enhanced tolerance on the part of the patient, there is an advantage in

split-dose therapy in that the fields of treatment can be larger than those often employed in conventional therapy. A review of the sizes of fields employed in the preceding 25 cases reflects not only the advanced stages of the lesions treated but also the freedom available to the author in treating "wide" of all detectable malignant tissues. It is my definite feeling that the large treatment fields possible with this method will materially lessen the incidence of "geographic misses," a most discouraging aspect of small-field radiation therapy.

POTENTIAL LATE COMPLICATIONS

The most significant reservation regarding the use of the split-dose system at present concerns the possibility of unexpected late reactions and complications, a potential hazard previously discussed.[19] The technique admittedly is an unfamiliar form of radiation therapy which employs complicated time-dose relationships, and much remains to be learned about its biologic effectiveness. Koller and Smithers[12] encountered an unusually high incidence of osteoradionecrosis when they used a type of split-dose therapy very similar to that employed by the author. To date, however, this complication has not been encountered in my series.

In spite of the obvious reduction in the severity of the immediate early reactions, there is some question as to whether the late effects of irradiation, such as scarring and fibrosis, protracted mucosal dryness, permanent epilation, radiation pneumonitis and so on are somewhat more severe than those which follow conventional therapy. To date, however, none of these side effects have been found severe enough to be considered a major or serious complication of periodic radiation therapy. Should it appear paradoxical to consider the possibility of lessened immediate postirradiation reactions as opposed to the potentially more serious and more severe late reactions, the reader is referred to the very astute observations of Chamberlain[2] by way of explanation.

The one major complication encountered in this series was a limited radiation myelitis which occurred in a patient who had received radiation therapy for the same malignant process of the parotid gland some years before. It would seem illogical, therefore, to ascribe the entire responsibility for this complication to the use of split-dose therapy alone.

SUGGESTIONS FOR FUTURE INVESTIGATION

Pending confirmation or rejection of periodic radiation therapy by other independent clinical trials, the future of the procedure would seem to lie in the development of some laboratory test which will reflect the ebb and flow of mitotic and metabolic activity under the changing stresses of interrupted radiation therapy. In spite of the promising early results obtained with this type of therapy, it is obvious that the basis for the selection of the time intervals for mitotic recovery of necessity is most empirical, at worst a frank guess and at best a conjecture based on the most rudimentary radiobiologic knowledge.

I believe that the most practical laboratory test indicator of mitotic flux eventually will prove to be an indirect one. Glücksmann[5] found that the peak of mitotic recovery coincides very well with the decrease in cellular degeneration after the initial phase of destruction. If the two are reciprocals of one another, meaning that if mitotic activity returns coincidentally with the cessation of cellular degeneration, then an indicator of cellular degeneration might reflect the optimal time for resumption of radiation therapy. It is well known that determinations of transaminase in the serum will accurately reflect massive cellular degeneration and breakdown such as occurs in the presence of myocardial infarction, dermatomyositis, hepatitis and other pathologic processes in which cellular destruction is maximal. Investigation is now under way to ascertain whether the determinations of transaminase will reflect the much more subtle and minor degrees of cellular breakdown associated with clinical

radiation therapy. If so, the test may eventually prove the ideal indicator for the optimal time for resumption of divided-dose radiation therapy.

Finally, it may be said that the philosophic concepts which evoked this venture into the use of split-dose therapy can be applied with even greater logic to the ever-growing field of chemotherapy. Whereas the radiotherapist's employment of maximal dosage is predicated on potential or excessive damage to the underlying tumor bed, the chemotherapist's maximal endeavors often are stayed by potential damage to the much more sensitive and more vulnerable hematopoietic system which is in essence the "tumor bed" of chemotherapy. The limitations of this comparatively new field are too well known for elaboration here. It is entirely possible, however, that the employment of properly spaced fractionated chemotherapy, timed so as to coincide with periods of increased tumor "susceptibility," may constitute a major advancement in many chemotherapeutic concepts.

A few outstanding examples of split-dose chemotherapy have been productive of results far better than those which would be expected from single or continuous therapy. Hatch, Bradford and Ochsner[6] in 1956, reporting on the use of nitrogen mustard in the treatment of advanced carcinoma of the lung, wrote that of 150 patients who received only one course of nitrogen mustard, 28 per cent exhibited some response, whereas of 48 patients who received more than one course, a symptomatic response of some degree was noted in 94 per cent. They therefore suggested repetition of the use of nitrogen mustard at regular intervals of eight weeks, regardless of the response to the first course.

Hertz *et al.*[7,8] have recently reported some very impressive results in the treatment of metastatic choriocarcinoma with methotrexate. The drug is employed either intramuscularly or intravenously in doses of 15 to 30 mg. per day for five consecutive days; then therapy is suspended until such time as hematopoietic recovery takes place. Therapy is then resumed and is continued intermittently, depending on hematopoietic recovery, until the values for chorionic gonadotropins decrease to nearly normal or until usually synonymously clinical recovery supervenes, or until toxicity of the drug or progressive malignancy precludes further therapy. The number of sessions employed in each of Hertz' patients varied from 1 to 15. Of 35 patients with metastatic choriocarcinoma, 9 exhibited striking clinical and hormonal remission for periods of three to thirty-three months, amazing results in a heretofore uniformly fatal disease. It is of interest to note that 4 of the 35 patients were not treated intermittently, meaning that single sessions only were used, and that all 4 died. Of the remaining 31 patients who were treated intermittently, only 9 obtained clinical remission of the disease, which is in itself a striking result. But even more remarkable, in 30 patients the decrease in values for chorionic gonadotropins was significant, implying a response to therapy far greater than was reflected in the number of clinical remissions.

Reese and associates[9,17] likewise have reported a very impressive rate of cure after the use of a type of divided-dose chemotherapy with triethylene melamine in conjunction with roentgen therapy for retinoblastoma. Since January, 1953, they and their co-workers have followed a policy of enucleating the eye most extensively involved with tumor and treating the remaining, less extensively involved eye with a combination of roentgen therapy and triethylene melamine. The exact details of the method are too complicated for reporting here, but in essence they involve the administration of a priming dose of triethylene melamine, initially given orally but now administered by the preferred intramuscular or intra-arterial route, followed by roentgen therapy to a tumor dose of approximately 3,250 r. This is followed, after a period during which hematopoietic depression is allowed to recover, by additional doses of triethylene melamine and then

treatment is continued at intermittent intervals, depending on the status of hematopoietic depression and the clinical course of the patient. The maximal number of treatments employed was seven. Reese and associates reported that they had been able to attain a cure rate of 90 per cent by the intramuscular or intra-arterial administration of triethylene melamine in association with roentgen therapy, a cure rate of 70 per cent with the oral use of triethylene melamine in association with roentgen therapy, and a cure rate of 60 per cent by use of the above methods for the more advanced lesions.

Neither Reese nor Hertz has stressed the factor of intermittency in the chemotherapy they employed, but it may be speculated if such striking results could have been obtained with continuous chemotherapy in single sessions. It may well be that, if these results can be reduplicated and enlarged upon and particularly if some laboratory test is forthcoming which will indicate tumor recovery rather than hematopoietic recovery (if the two are not indeed synchronous), perhaps the concept of split-dose or periodic therapy will prove an even greater advance in chemotherapy than the advance the author expects it will afford radiation therapy.

CONCLUSIONS

A relatively little-known modification of time-dose relationships—that of split-dose or periodic radiation therapy—and a consideration of the potential usefulness of the method in clinical radiation therapy have been presented. The early encouraging results in the treatment of the first 25 patients with far-advanced malignant processes of the head and neck have been reviewed and the technique of therapy has been discussed. The apparently increased effectiveness of periodic therapy, in company with the less severe immediate sequelae of irradiation and the greater tolerance of the patient to this type of therapy, makes the technique a departure from conventional radiation therapy practice, warranting additional investigation from both the research and clinical aspects.

Mayo Clinic
Rochester, Minnesota

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THE DIFFERENCES IN RESPONSE OF GRAFTED AND NORMAL SKIN TO IONIZING IRRADIATION*

CLINICAL OBSERVATIONS

By PHILIP RUBIN, M.D., *and* CAPT. JERRY W. GRISE, USAF, MC†
ROCHESTER, NEW YORK

ONE of the unwritten but commonly stated concepts in radiation therapy is that grafted skin tolerates irradiation poorly. Since reconstructive surgery is increasing with the advent of more radical surgical procedures for various carcinomas, postoperative irradiation of grafted sites is not unusual. Recently, Cram, Weder, and Watson,[1] concerned that patients with malignant disease who have skin grafts might be denied roentgen therapy, presented a study on postmastectomy irradiated grafts. It was their conclusion that the tolerance of skin grafts to radiation therapy approximates that of normal skin.

Since no bibliography was presented and no other documentation of clinical observations is available in the literature, our experience is recorded, as the conclusions differ from those of the aforementioned authors in that we noted very definite differences in the reactions of normal and grafted skin sites to ionizing irradiation. Despite this seeming contradiction, careful analysis of the data suggests that the study of Cram *et al.* may be complementary, since different factors were used. It is hoped that this report will stimulate further interest in this problem when it is encountered clinically and will increase the awareness of the radiotherapist to the fact that differences do exist.

Our interest in this subject began two years ago when a patient with an extensive facial graft required irradiation for uncontrolled recurrent carcinoma. The course of therapy was instituted with reluctance since the carcinoma was radiation induced and a significant portion of grafted skin had to be incorporated in the treatment field. Careful documentation and photography were done in anticipation of an unusual sequence of reactions. This proved to be the case, with an inadvertent and tragic ending. After this experience, every patient with a grafted site who was irradiated was carefully followed.

REPORT OF CASES

CASE 1 (Fig. 1 and 2, *a–e*). E.M., 63033, a fifty-five year old white man, received "twelve x-ray treatments" for acne when he was eighteen years of age. At the age of thirty-one, he received "three more x-ray treatments." The factors are not known. When seen at Strong Memorial Hospital in 1950, the skin of the face, with the exception of the forehead, was covered with numerous keratotic areas. Due to the severe, chronic radiodermatitis, replacement of facial skin by grafts was deemed necessary. In the ensuing five years, the patient had numerous facial split thickness grafts until the skin of the nose, cheeks, and chin was replaced. The nose was reconstructed partially with a cervical tube pedicle graft. A number of basal cell carcinomas on the face required excision during the same five years (Fig. 2*a*).

In 1957, a squamous cell carcinoma of the right buccal mucosa developed with metastases to the right submandibular region requiring excision and replacement by split thickness skin graft of the right buccal area. A right suprahyoid neck dissection was also done. Recurrence five months later in the left anterior cervical chain necessitated a left radical neck,

* From the Division of Radiation Therapy and Radioisotopes, Department of Radiology, Strong Memorial Hospital, Rochester, New York.

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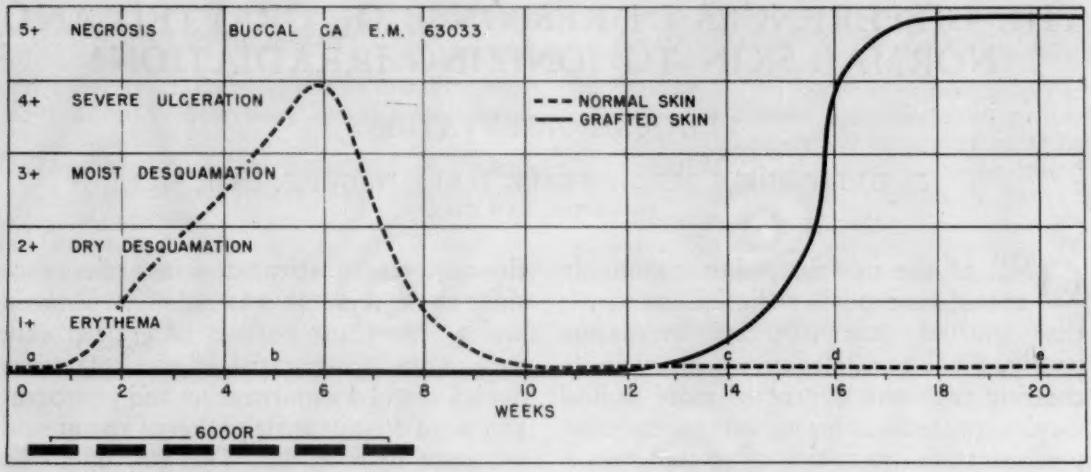

Fig. 1. Case 1. Graph showing the course and intensity of normal and grafted skin reactions following exposure to radiation. Old grafted skin did not respond as vigorously as normal skin initially but, once it did respond, it failed to demonstrate any power of recovery and went on to necrosis.

dissection. Recurrence two months later was along the edge of the skin graft on the right buccal mucosa with extension into the superior buccogingival gutter, parotid gland region, and right neck.

A depth dose of 6,214 r was delivered by 1

Fig. 2. Case 1. (*a*) The grafted skin mask is shown prior to radiation therapy. (*b*) Grafted skin shows no reaction, whereas normal skin is reacting briskly. (*c*) Full recovery is evidenced by normal skin; graft shows initial softening. (*d*) Necrosis of the graft begins. (*e*) Late necrosis of the graft is demonstrated.

mev. radiation, half-value layer 9 mm. Cu, utilizing a single 10×10 cm. field to the recurrent tumor. The port included the principal portion of the right buccal graft. Therapy was extended over forty-one days. The graft in the treatment field showed no reaction during irradiation (Fig. 2*b*). The adjacent normal skin reacted briskly and recovered within two months (Fig. 2*c*). Sixteen weeks after the beginning of radiation therapy, the graft rapidly necrosed forming an oral-cutaneous fistula (Fig. 2 *d* and *e*). The patient died one month later, hemorrhaging from a carotid artery branch in the right neck.

Comment. The response of the normal skin in the treatment field seemed rapid and brisk in onset considering the fact that 1 mev., half-value layer 9 mm. Cu radiation was employed. This peaked at the conclusion of therapy and rapidly subsided. The grafted site, in sharp contrast, showed no reaction and tolerated the entire course extremely well. Five weeks after completion of treatment, the normal skin was fully recovered but a very slight erythema began to appear and progress in the grafted area. This turned deeply red and rapidly necrosed at the sixteenth week. Thus, old grafted skin did not respond as vigorously as normal skin initially but, once it did respond, it failed to demonstrate any power of recovery and went on to necrosis.

Case II (Fig. 3). A.R., 187176, a fifty-six year old white man, had a laryngectomy and right radical neck dissection for squamous cell carcinoma of the larynx in 1956. A split thickness graft was placed in the cervical area for plastic reconstruction because of numerous postoperative complications.

Two years later, the patient was found to have a large ulcerated lesion in the left half of his tongue, with extension to the floor of the mouth and posteriorly to the palatine tonsillar fossa. Biopsy showed squamous cell carcinoma.

The patient received palliative 1 mev. irradiation, half-value layer 9 mm. Cu, utilizing opposed 10×10 cm. ports. The port dosage was biased 2:1 to the left. A total tumor dose of 5,000 r was delivered over a thirty-nine day period. During the course of therapy and thereafter, the graft showed no reaction. In the three months after completion of therapy, the tongue carcinoma showed complete regression on physical examination. Since then, however, the disease has recurred in the sublaryngeal area and at the base of the tongue.

Comment. A biased port arrangement was utilized which favored the distribution of dosage to the site of tumor involvement. The reaction in the normal skin site at a dose of 4,300 r was a mild to moderate erythema with dry desquamation at the conclusion of therapy. No discernible reaction was noted in the grafted skin site; the whiteness of the graft was apparent, surrounded by reacting normal skin. After a

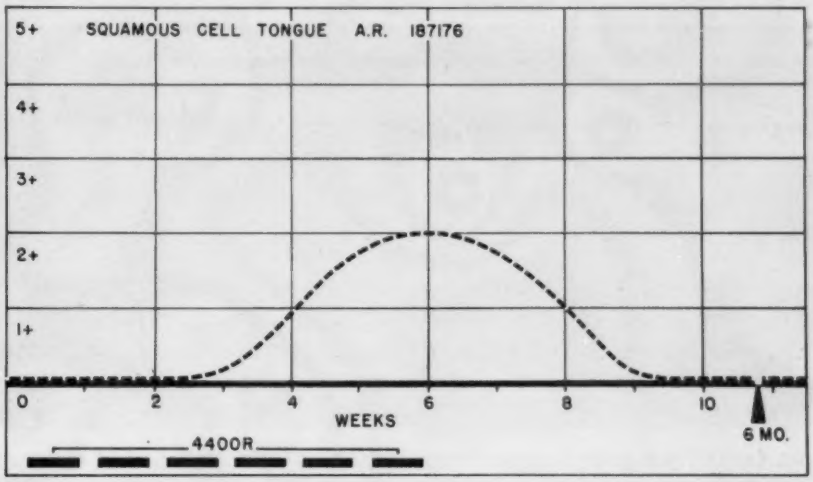

Fig. 3. Case II. Old grafted skin did not react to irradiation as did normal skin. No late necrosis was observed.

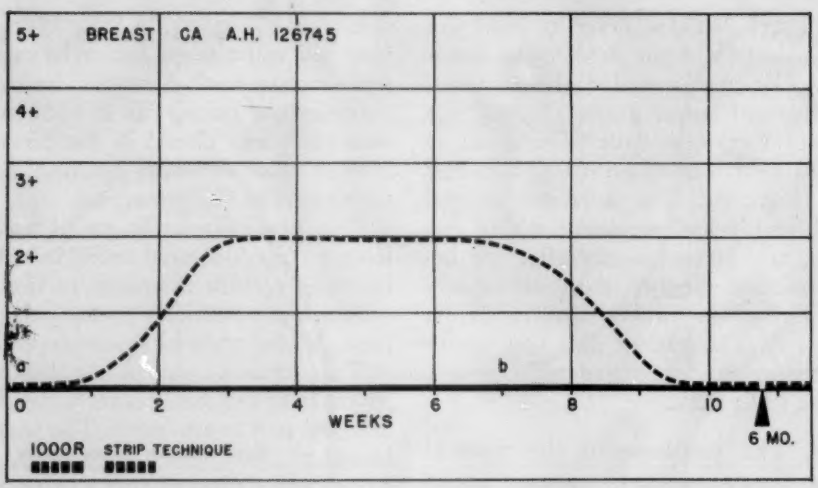

Fig. 4. Case III. Old grafted skin did not react at all to short, intense, superficial irradiation but normal skin did.

follow-up period of six months, the grafted skin has shown no change. Thus, old grafted skin did not react to irradiation as did normal skin. No late necrosis has been noted with the lower dose employed.

Case III (Fig. 4 and 5, *a* and *b*). A.H., 126745, a sixty-five year old white woman, had a radical left mastectomy in October, 1952, for carcinoma of the breast. A rather large split thickness graft was used in obtaining closure. The pathologic specimen showed no microscopic metastases in the left axilla. Yearly follow-up examinations were negative until November, 1958, at which time multiple small tumor implants were found on and adjacent to the skin graft. These were treated with 112 kv., half-value layer 3.7 mm. Al radiation utilizing a strip technique. Single doses of 1,000 r were given to each skin strip.

Comment. Single large doses, rather than a fractionated schedule, and lower energy irradiation (112 kv. in contrast to 1 mev.) elicit a greater reaction in normal skin. Theoretically, the reaction in grafted skin likewise might be more vigorous. As expected, normal skin began reacting at the beginning of the second week and went on to dry desquamation with full recovery in nine weeks. The grafted skin site was sur-

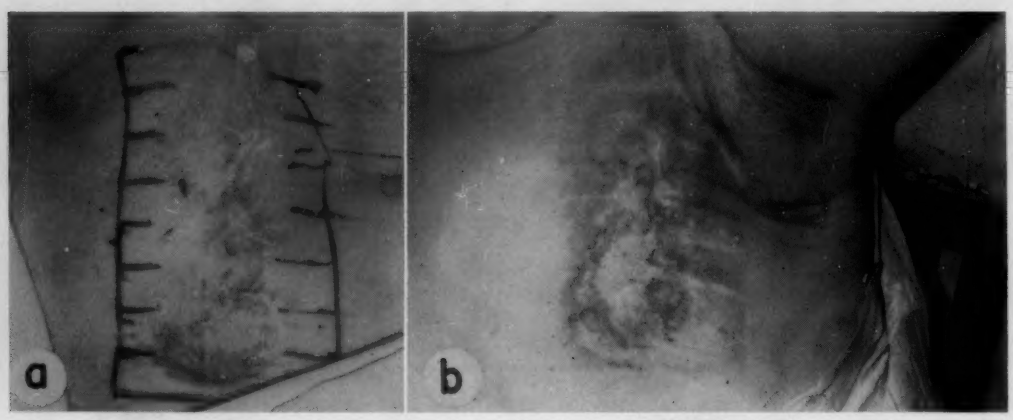

Fig. 5. Case III. (*a*) Old skin graft is shown before irradiation with strips marked for treatment. (*b*) The large, irregular graft shows no reaction and is surrounded by normal skin reacting with erythema and dry desquamation.

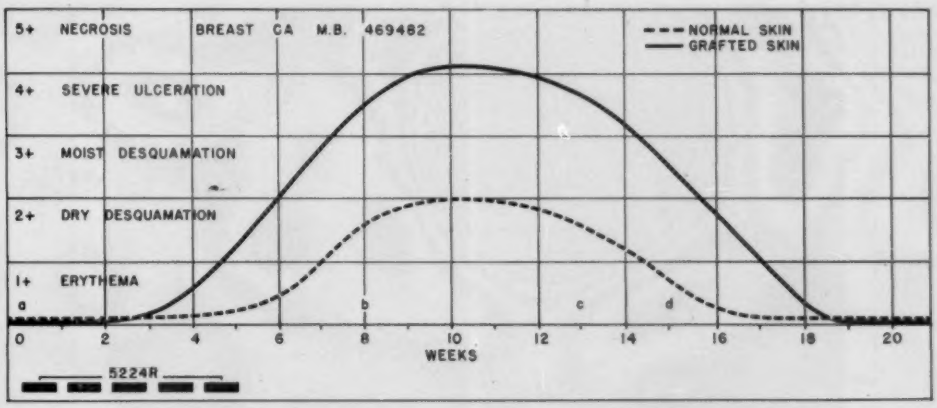

Fig. 6. Case iv. Newly grafted skin was more sensitive to irradiation than normal skin in terms of early reaction, severity of reaction, and delayed recovery.

rounded by a halo of erythema and later pigmentation. After six months of follow-up, no evidence of change in the grafted site has been noted. Thus, old grafted skin did not react at all to short intense superficial irradiation as did normal skin. No late changes have been observed.

Case iv (Fig. 6 and 7, *a–d*). M.B., 469482, a sixty-six year old white woman, noticed a "lump" in the lower medial quadrant of her right breast in February, 1959. She brought this immediately to medical attention and radical mastectomy was performed in March, 1959. A split thickness graft was necessary for closure. The pathologic specimen showed carcinoma with no evidence of metastases in the right axillary lymph nodes.

In April, 1959, the patient received postoperative 1 mev. irradiation, half-value layer 9 mm. Cu, utilizing opposed 10×15 cm. ports to the right supraclavicular and axillary areas and an anterior 6×10 cm. port to the right internal mammary chain. The 6×10 cm. port included virtually all of the graft which was needed for skin closure at the time of radical mastectomy.

Comment. The skin in our routine internal mammary port can tolerate a dose of 5,000 r to 6,000 r with 1 mev. irradiation with moderate erythema and dry to slightly moist desquamation as the usual sequence of reactions. This reaction started in this patient at the beginning of the third week and peaked a week after the conclusion of therapy. The grafted skin strikingly responded earlier and more vigorously to irradiation. After the second week, the reaction began at the margin of normal and grafted skin in a small area of denudation along the inferior peripheral border. It extended into the center of the graft until the entire graft had ulcerated. This entire course was the reverse of our previous experience with older skin grafts. Complete healing of the grafted zone was noted on the eighteenth week. Thus, newly grafted skin was more sensitive to irradiation than normal skin in terms of the early reaction and delayed recovery.

Case v (Fig. 8). C.O., 36403, a fifty-one year old white woman, noticed a lump in her left breast in December, 1958. Radical mastectomy was performed at Strong Memorial Hospital in January, 1959, and for closure it was necessary to use a split thickness skin graft. The pathologic specimen showed carcinoma with the superior axillary lymph nodes being virtually replaced by tumor. Postoperative 1 mev. irradiation, half-value layer 9 mm. Cu, was instituted one month after surgery. The left supraclavicular and axillary areas were treated with opposed 10×15 cm. ports and the left internal mammary lymph nodes were treated with an anterior 6×10 cm. port. The 6×10 cm. port included only a small margin of the graft used for closure. A skin dose of 5,100 r delivered 4,600 r to the internal mammary lymph node chain. A midline tumor dose of 5,000 r was given to the left supraclavicular area.

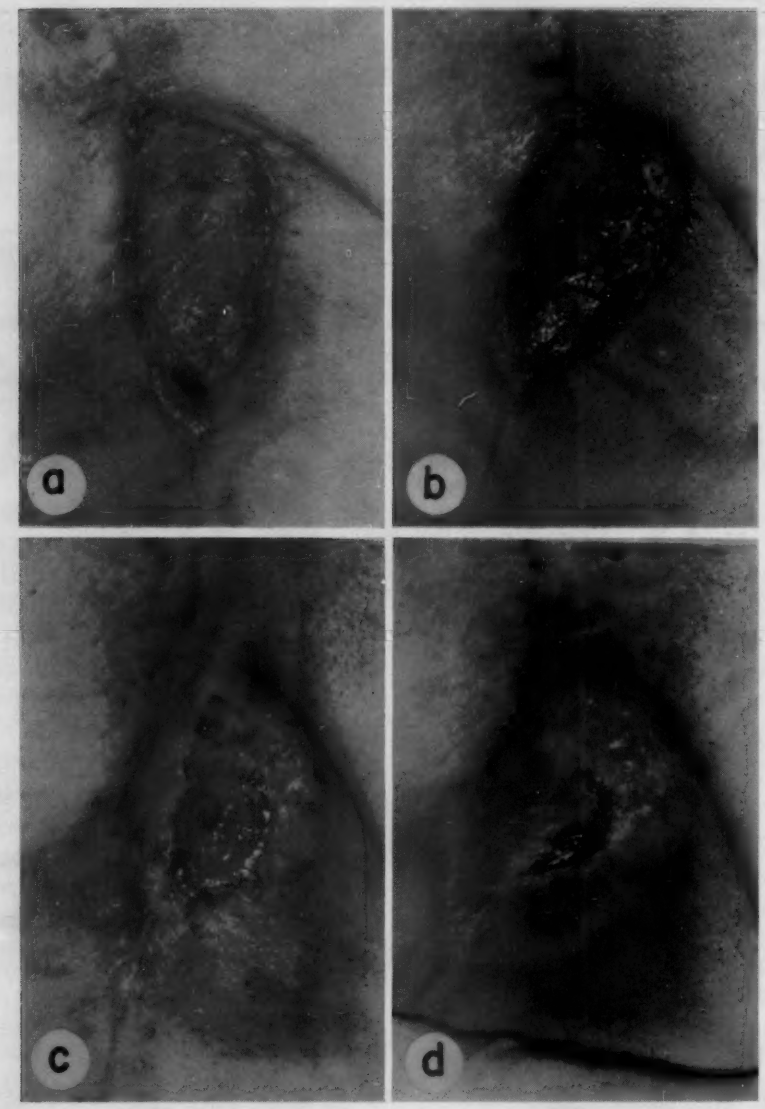

Fig. 7. Case IV. (*a*) Appearance of the graft at the beginning of radiation therapy is shown. (*b*) Graft is approaching ulceration. (*c*) Healing phase of the graft is demonstrated. (*d*) Healing is virtually complete in the graft.

Comment. In a treatment schedule and setting similar to Case IV, normal skin in this instance was reacting somewhat earlier and more briskly than the newly grafted skin. This initial difference was very slight and probably was due to the fact that only a small zone of the treatment field was occupied by the grafted skin. At the time the erythema began, it occupied the junctional margin between normal and grafted skin. The site of denudation and ulceration started in the graft margin and extended across into the adjacent normal skin at the conclusion of treatment. Healing and recovery were definitely slower in the grafted site compared to the normal skin. Thus, in new postmastectomy graft sites, a similar response in normal and grafted sites was noted where only a corner of the grafted area was in the treatment field, but a definite delay in recovery of the grafted skin was also observed.

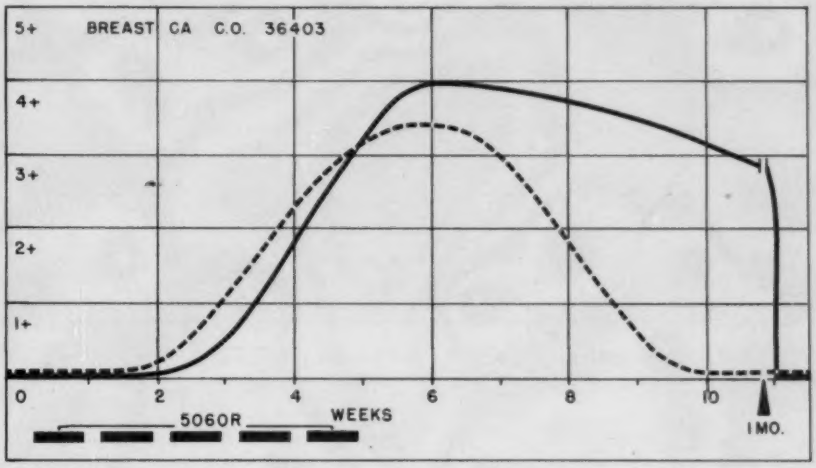

FIG. 8. Case v. A similar response in normal and newly grafted skin was noted when only a corner of the grafted area was in the treatment field, but a definite delay in recovery of the grafted skin was also observed.

CASE VI (Fig. 9 and 10, *a* and *b*). M.W., 417167, a fifty-six year old white woman, noted a lump in her left breast one week before admission to Strong Memorial Hospital on June 7, 1956. On June 9, a radical mastectomy was performed. The pathologic specimen revealed carcinoma with gross and microscopic metastases to the axillary lymph nodes. A split thickness graft was necessary for closure. Two months after surgery, 1 mev. irradiation, half-value layer 9 mm. Cu, was initiated. The left supraclavicular and axillary areas were treated utilizing opposed 10×15 cm. ports and the left internal mammary lymph nodes were treated with an anterior 6×15 cm. port. This latter port included a margin of the graft used for closure. A two year follow-up has revealed no evidence of recurrent disease.

Comment. This case is included, though not studied originally, because of the long follow-up of two years. As in Case v, the corner of a postmastectomy graft was irradiated through the internal mammary field. Normal and grafted skin reacted in a similar fashion with the reaction appearing slightly earlier in the normal zone, which may be due to a volume factor. At the completion of treatment, the reaction was of

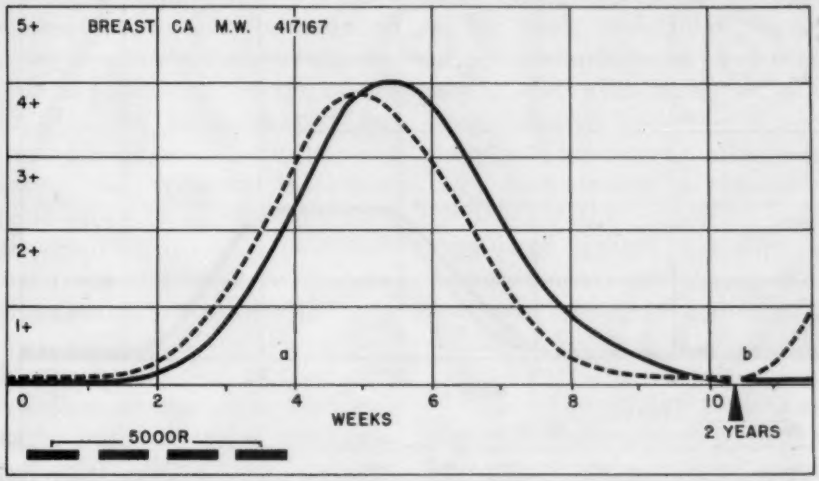

FIG. 9. Case VI. Grafted skin does not show the late changes of telangiectasia as seen in normal skin

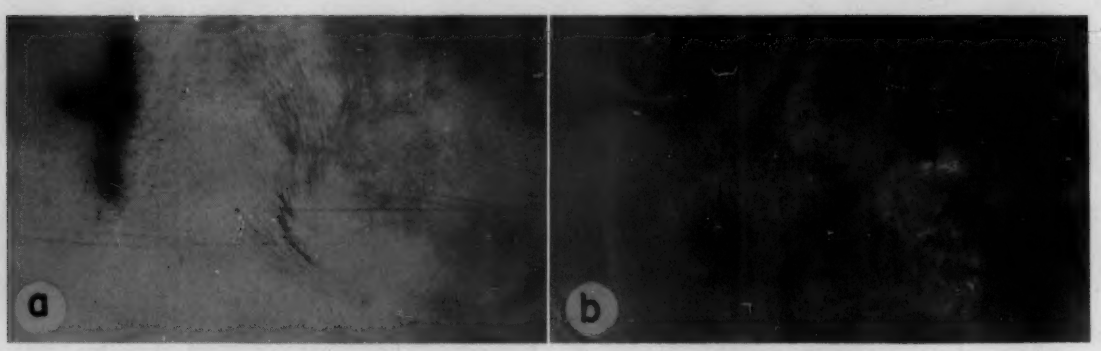

Fig. 10. Case vi. (*a*) Normal and grafted skin reacted in a similar fashion with the reaction appearing slightly earlier in the normal zone. (*b*) Telangiectasia involves only normal skin and not the graft.

similar intensity and recovery was quite parallel. As a late follow-up finding, telangiectasia was quite prominent in both the internal mammary and supraclavicular fields, except for the corner of the grafted zone in the internal mammary field which remained flat and white with no telangiectasia. Thus, grafted skin did not show the late changes of telangiectasia as seen in normal skin.

Case vii (Fig. 11 and 12, *a–c*). H.Z., 472517, a forty-eight year old white woman, had bilateral popliteal skin nevi resected in August, 1957. Subsequently, she developed lymphadenopathy in the left inguinal area and a left radical inguinal lymph node dissection was done in February, 1958. Local recurrence in the left popliteal area required excision in August, 1958. In February, 1959, further excision in the left popliteal area required a full thickness skin graft.

In May, 1959, lymphatic seeding was evident. Multiple small metastases on the anteromedial aspect of the left leg were found. Treatment with 280 kv. irradiation, half-value layer 1 mm. Cu, was given utilizing a progressive strip technique. Each 2 cm. width of skin was treated with the port overlapping half of the previously irradiated, adjacent strip. A total dose of 2,400 r divided into four equal doses of 600 r was given to all areas of skin involvement, including the grafted site.

Comment. The reaction in normal skin was that of dry desquamation. This was limited to a zone of 3–5 cm. and gradually spread down the extremity. The grafted

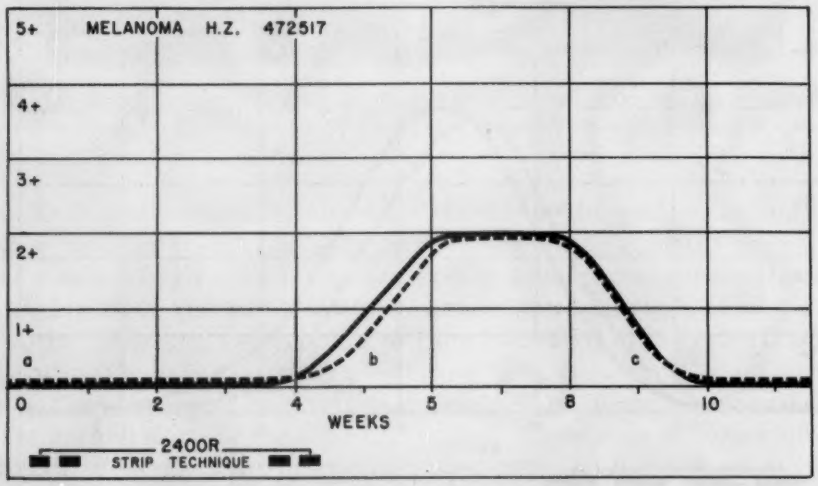

Fig. 11. Case vii. Grafted skin in the transitional phase between old and new grafts reacts in a similar manner to normal skin.

FIG. 12. Case VII. (*a*) Graft is shown before irradiation. (*b*) Normal skin shows reaction extending down the medial aspect of thigh. (*c*) Dry desquamation of both normal skin and the medial portion of the irradiated graft is shown.

skin reacted as did normal skin in time and degree. Thus, grafted skin in the transitional phase between old and new grafts reacted in a manner similar to normal skin.

DISCUSSION

From the clinical observations presented, it can be concluded that differences in the pattern of response and recovery to ionizing irradiation occur in grafted skin sites as compared to normal skin. There is a spectrum of response ranging from pronounced radiosensitivity to relative radioresistance. The reactivity is related to the age of the graft. Clinically, the radiotherapist encounters situations which fall at either end of the spectrum; *i.e.*, recurrent disease in an older graft or residual neoplasm in a freshly grafted site.

In reviewing the graphs of the skin responses, the following discernible patterns are seen:

1. *A graft older than one year is more radioresistant than normal skin.* In Cases I, II and III the initial response to irradiation, as commonly recognized, did not occur; *i.e.*, the erythema and eventual dry to moist desquamation seen in adjacent normal skin were lacking. On the basis of these cases, one might be led to believe that grafted skin is more resistant to irradiation in similar settings and doses than normal skin.

The one instance in which late necrosis supervened in the grafted site (Case I) first began reacting three to four months after beginning therapy. This was after the normal skin had completely recovered from a rather brisk, moist, desquamative epithelitis. Fortunately, this has not occurred in any of the other cases, all of which have been followed for at least six to twelve months. There were a number of extenuating circumstances in this case which included a rather extensive carcinoma and very large grafted skin sites. In fact, the buccal mucosa underlying the skin graft had been replaced by another graft giving a unique situation of a skin graft and buccal graft *vis-à-vis*.

2. *Fresh grafts (up to three months) react earlier and more vigorously than normal skin.* Our experience with fresh postmastectomy grafts was the reverse of our initial experi-

ence, in which grafted sites were more than a year old. In Case IV, there was no doubt that the epithelitis of the graft started earlier, was brisker, more ulcerative, and took longer to heal than that of the adjacent normal skin. Curiously, the reaction began at the margin of the normal and grafted skin, then spread to the center of the graft. Healing was similar to that in normal skin with central islands of epithelium spreading out, coalescing and eventually completing repair.

In Cases V and VI, the similarity of reactions in normal and grafted skin was quite interesting but may reflect marked differences in the volume of the areas exposed to irradiation. In both cases, only a few square centimeters of grafted skin were included in the corner of the treatment field. Usually, the skin reactions fade rapidly in the inferior and lateral corner of the internal mammary field. The fact that this graft site reacted as much as the center of the field suggests some increased reactivity of the graft site.

3. *Recovery phenomena are delayed in fresh grafts and absent in old grafts.* In the first case, the inability of the old graft to recover is evidenced by the development of late necrosis. It was a most unusual situation in that the response and recovery aspects of the typical radiation injury seemed to be separated. Fortunately, this situation appears infrequently and only when factors such as excessive scarring and extensive carcinoma are present in addition to the large doses employed. In fresh grafts, the healing of ulcerated areas is usually slower than in normal skin; however, no late reactions of necrosis have been encountered clinically.

4. *Similarity in tolerance of normal and grafted skin occurs during the transitional phase (three months to one year).* Case VII, the only case in which the graft was in the transitional phase, had a response quite similar to that of normal skin. By utilizing the strip technique of irradiation and considerable fractionation, different response patterns would have been easy to separate and identify. The reactive epidermitis gradually crept down the extremity and the desquamation on the normal and grafted skin sites was identical. One might estimate that the transitional period from a fresh to an old graft is from three to twelve months after the skin is transplanted.

These observations raise the following questions:

A. Why is there a difference in the radiation reaction of the grafted skin site as compared to normal skin? The difference in the blood supply to normal skin and to grafted skin might form a reasonable basis for explaining the differences in the reactions.[5] To evaluate the changing pattern of the blood supply to an autograft,[2,3] a brief review of the histologic changes following transplantation of skin was presented in another paper.[6]

B. Do the differences in the reactions of grafted skin to irradiation constitute a contraindication to radiation therapy in malignant disease? On the basis of our experience and that of others, it is not felt that the graft tolerance is a serious complication in the course of therapy. If one anticipates the difference in reaction and prepares the patient and the referring surgeon, both may be spared moments of apprehension. Except for 1 case of late necrosis, which was a multifaceted problem, all of the grafted sites recovered slowly but completely.

The complexity of the problem obviates drawing up a set of rules which apply in all circumstances. Individualization is important as a variety of factors exists which influences the reaction of the graft to irradiation. Although it has been theorized that the degree of vascularity is a central consideration, other factors remain to be analyzed. Since it is impossible to explore all the variables on patients, an experimental program was undertaken. In a separate report,[4] the effects of irradiation on pig skin autografts were presented to define such

factors as: (1) the quality of the irradiation; (2) the age of the graft at time of irradiation; (3) fractionation and protraction of dose; and (4) split and full thickness grafts. On the basis of these observations, therapeutic implications were developed.

SUMMARY

From the clinical observations presented, it can be concluded that differences in the pattern of response and recovery to ionizing irradiation occur in grafted skin sites. It is also apparent that there is a spectrum of response ranging from pronounced radiosensitivity to relative radioresistance. The reactivity is proportional to the age of the graft.

1. In old grafted sites (more than one year old), the graft is more radioresistant than normal skin.

2. In freshly grafted sites (usually within three months of grafting), the grafted skin reacts earlier and more vigorously than normal skin.

3. Recovery phenomena are delayed to absent in fresh and old grafts, respectively.

4. A similarity in the tolerance of normal and grafted skin occurs during the transitional phase (three months to one year).

Philip Rubin, M.D.
Department of Radiology
Strong Memorial Hospital
260 Crittenden Boulevard
Rochester 20, New York

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LYMPHOSARCOMA, RETICULUM CELL SARCOMA AND GIANT FOLLICULAR LYMPHOMA*

LONG TERM RESULTS FOLLOWING RADIATION THERAPY

By J. C. COOK, M.D., K. L. KRABBENHOFT, M.D., *and* T. LEUCUTIA, M.D.
DETROIT, MICHIGAN

LYMPHOSARCOMA has been known as a separate entity since its description by Kundrat[27] in 1893. Prior to that time it was grouped with several other conditions under the title of pseudoleukemia. The high degree of radiosensitivity of this malignant tumor was determined soon after the discovery of the therapeutic potential of roentgen rays. One of the earliest descriptions of the use of roentgen therapy was that reported by Pusey[34] in 1902. This report deals with the treatment of cases of sarcoma (some of them lymphosarcoma) and Hodgkin's disease. Following further development of roentgen therapy techniques, this modality has been accepted as the preferred method of treatment for the majority of the patients afflicted by lymphosarcoma and the closely allied conditions of reticulum cell sarcoma and giant follicular lymphoma.

Complete records and careful follow-up studies of all therapy patients have been made at Harper Hospital since 1922 and it is the purpose of this paper to present the long term results in a series of cases of lymphosarcoma, reticulum cell sarcoma and giant follicular lymphoma in which roentgen therapy was the sole method of treatment, except in a few instances where it was the primary method of treatment. The analysis includes a classification of these patients as to age, sex and stage of disease. When the number of cases is statistically significant, various percentage survival rates and average survival times of expired patients are presented. Also presented is the treatment technique used in obtaining the remissions and palliations described.

MATERIAL AND CLASSIFICATION

The entire series of lymphosarcoma, reticulum cell sarcoma and giant follicular lymphoma treated from 1922 to mid 1958 comprises 514 cases. The survival dates are computed from the time the patient was first referred for roentgen therapy until the time of death or until the patient was lost to follow-up. There have been no exclusions because of loss to follow-up and such patients are presumed dead. Of the entire group only 56 cases, or 10.8 per cent, were lost in this manner, and these were followed for an average of 47.3 months before they became untraceable.

Prior to the description by Brill, Baehr and Rosenthal[2] in 1925, followed closely by that of Ikeda[24] in 1926 and Symmers[38] in 1927, the giant follicular lymphoma was not recognized as a separate entity. Our first treated case with such a diagnosis was referred on February 10, 1936, and there is a total of 55 cases in our series. A similar situation exists with regard to reticulum cell sarcoma, of which we have treated 114 cases since 1931. The diagnosis was not extensively made until the time of the reports of Ewing,[13] Roulet[35] and Callender.[3] Other cases of reticulum cell sarcoma may be included in the total of 345 cases of lymphosarcoma, particularly those referred prior to 1931. Unfortunately, not too infrequently it is impossible to make an absolute differentiation of the various types of malignant lymphoma;[15,17] even microscopic sections from the same patient procured at different times may result in different tissue diagnoses. This led Elkins[11] to state that, because of the interchangeable nature of the pathology of these diseases, statistics

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based on cell type must be regarded with some skepticism as to their validity.

The rather simplified nomenclature of lymphosarcoma, reticulum cell sarcoma and giant follicular lymphoma has been used because it is that most generally accepted and understood. It is recognized that all three forms, whether they are disseminated by metastases to the lymphoid system, by independent blood-borne emboli, by circulating toxins or by direct extension, will, if untreated, progress to generalization and death of the patient.

Cantril[4] has observed that lymphosarcoma is more apt than Hodgkin's disease to involve any or all tissues, thus producing clinical manifestations of the most complex nature. Sugarbaker and Craver[37] have stated, "Lymphosarcoma is a malignant disease of lymphoid tissue capable of arising in any lymphoid aggregate. It may run an acute or chronic course and is invariably radiosensitive." They also stated that the use of the term "lymphoblastoma" is a defeatist approach, since it comprises 13 or 14 entities. Lenz *et al.*[29] defined lymphosarcoma as an invasive metastasizing growth originating in lymphoid and reticulum endothelial cells, which in approximately two-thirds of the cases has its primary site in the lymph nodes and in about one-third in extranodal locations. Table 1 gives the location of the primary site of the 514 cases being reported. In 172 patients we were unable to determine the site of origin because of generalized involvement. Cutler[8] made the observation that the actual distribution of the disease is nearly always wider than the clinical observation discloses.

Staging, for these reasons, is difficult and may be inaccurate. In this paper an attempt has been made to stage the reported cases only on the basis of relative localization or generalization at the time of referral. Thus, Stage I includes involvement of a single lymphatic region, or two or three proximal lymphatic regions, but without symptoms of generalized disease. Stage II includes detectable clinical involvement of two or more proximal lymphatic regions with symptoms of generalized disease, or involvement of two or more distant lymphatic regions. The division into two stages was also used because our initial treatment technique was essentially based on localized or generalized involvement.

Table I

LYMPHOSARCOMA, RETICULUM CELL SARCOMA AND GIANT FOLLICULAR LYMPHOMA

Location of Primary Site	No. of Cases
Generalized Involvement	172
Cervical Lymph Nodes	84
Abdominal Lymph Nodes	51
Axillary Lymph Nodes	33
Mediastinal Lymph Nodes	27
Tonsil	24
Inguinal Lymph Nodes	15
Salivary Glands	20
Nasopharnyx	14
Bone	6
Small Bowel	13
Large Bowel	11
Stomach	11
Mesentery	13
Orbital Area	5
Miscellaneous	15
Total	514

TECHNIQUE OF ROENTGEN THERAPY

As already stated, in all cases reported, roentgen therapy was the primary method of treatment and, in the majority, the only definitive treatment. Conventional equipment consisting of machines with 200 kv. peak output, 1 mm. Cu filtration, and a half value layer of 1 mm. Cu was used in all early cases. More recently, 225–250 kv. constant potential with Thoraeus filtration and a half value layer of 3 mm. Cu was employed. Those patients with mediastinal involvement were treated with roentgen rays generated at 500 kv. constant potential, 7 mm. Cu filtration and a half value layer of 9 mm. Cu. This was done to minimize pulmonary fibrosis and obtain a higher percentage depth dose. Our present method

employs the 2 mev. Van de Graaff type generator with 7.6 mm. Pb filtration and a half value layer of 8 mm. Pb in place of the 500 kv. constant potential equipment for mediastinal involvement.

In the treatment of such a serious group of malignancies with many variable factors, a large measure of the success obtained can be attributed to the careful observation and treatment planning of each case as an individual problem. For this reason it is impossible to give a detailed account of the various techniques employed. Generalizations, however, can be made: (1) prolonged fractionation with large total tumor doses is usually neither desirable nor necessary; (2) a repetition of the original treatment series at least once, and occasionally twice, after an interval of two months between each series and with a slightly lesser tumor dose is beneficial; (3) long term results are difficult to obtain by the so-called "chasing technique" and are most often procured by supplementary irradiation of the adjacent lymph nodes in the Stage I cases and of the greatest part of the lymphatic system as well as of the known areas of manifest involvement in the Stage II, or generalized, cases; (4) in selected cases and in certain locations, supervoltage radiation therapy is helpful but has no advantage in most treatment planning; and (5) frequent and careful observations are necessary at regular intervals, using all diagnostic and supportive therapeutic measures both during and immediately following prescribed treatment.

The above generalizations deserve amplification and may warrant explanation. Fractionation, usually with daily increments of 200 r in air to each area of involvement, has been recommended by several authors,[4,19–21,29,31] particularly in localized lesions, with a total tumor dose of 2,000 r[31] to 5,000 r.[29] More rapid administration with lesser total tumor doses is suggested by others.[14,18] Most agree that large fields should be used.

Fractionation has been employed in this series in the treatment of individual manifestations of Stage I cases and in uniregional involvement by giant follicular lymphoma. The majority of patients with Stage I disease are treated by massive technique with the administration of a tumor dose to superficial lymph nodes of 700 to 800 r at one seance. In the patients with deep pelvic or abdominal involvement, when cross-firing is necessary four or five large portals are used, each treated on successive days, for a total tumor dose of 1,200 to 1,600 r in the four to five day period. The treatment of the known area of involvement is supplemented by treatment of the adjacent lymph node areas.

In the Stage II cases, fractionation is rarely used but treatment is given to most lymph node areas, as was early advocated by Gilbert and Sluys.[18] The same massive methods are used as described above for Stage I cases except that ten to fourteen large portals are treated in as many days. Each portal is treated but once during the series. This allows practical treatment of even moderately advanced cases, which is not obtained by fractionation of the dose to each area. The areas treated include each cervical and supraclavicular area, each axilla, the abdomen and pelvis (which are cross-fired), and the mediastinum (for which there is the addition of the supervoltage technique). The total amount of radiation is much less and the response of the tumors is more rapid than with prolonged fractionation.

Depending upon the response of the disease to the original series of treatment and the general condition of the patient, blood findings, chemical balance and other evidence of general recovery, this original series is usually repeated at an interval of two months with a slightly decreased dose. In an exceptional case a third series may be necessary. Here the treatment is directed to clinically observed areas of persistent involvement. The time interval allows for recovery of the host and only incomplete recovery of the tumor cells. A second series completes the sterilization of the tumor

tissue in responsive cases. Most of these highly radiosensitive tumors are not clinically perceptible four weeks after the original series. However, attention must be directed to the fact that, with a group of malignancies so diversified in their areas of involvement and so variable in their manifestations as well as in their response to irradiation, the therapist must be familiar with all applicable methods and be prepared to use them, or resume their use, depending upon the individual case and its response or lack of response to any single method.

The application of radiation therapy to large areas of the body as well as the seriousness of the diagnosis necessitates careful observation and continued re-evaluation of each patient. During and immediately following the period of active therapy, constant vigilance is imperative. Antiemetic and tranquilizing medications are employed during the course of treatment. The white blood cell count is usually markedly lowered in the first three weeks, followed by a temporary anemia. Restricted activity, the use of antibiotics and, occasionally, blood transfusions or adjustment of the chemical and water balance are necessary. In the weeks, months and years after the original treatment, frequent checkup observations are desirable to record the result of treatment, to promote the patient's general well-being and to detect evidence of recurrence or new manifestation of the disease. In the event of recurrence, the technique described is not so destructive that additional curative therapy may not be given, if necessary, even to previously irradiated areas. An illustration of what can be accomplished by careful follow-up and repeated treatment is the case recently reported by Hummon *et al.*[23] in which a patient with follicular lymphoma had treatment to thirty-eight different portals over a period of four years with a total air dose of 43,328 r. There was no bone marrow damage and the patient has survived for at least three years after cessation of treatment.

SURGERY AND CHEMOTHERAPY

Surgery in the present series of cases has only been used for procuring biopsy material, and in a limited number of cases (41) for removal of bulky tumor masses prior to the institution of roentgen therapy. Surgery has been advocated in certain selected cases by Jackson[25,26] and by Gall and Mallory[14] for lesions localized to a viscus or bone. Diamond[10] states that surgery is only used in special situations in early cases and then often is followed by roentgen therapy.

Chemotherapy has been less helpful in the treatment of lymphosarcoma, reticulum cell sarcoma and giant follicular lymphoma than it has been in the treatment of Hodgkin's disease. Tod[39] also found this to be true and stated that Hodgkin's disease is the only entity in the lymphoma group which consistently shows response to treatment with nitrogen mustard. Craver[6] feels that nitrogen mustard has only contributed to palliation in these conditions. When given, nitrogen mustard is administered in the amount of 0.1 mg. per kg. of body weight daily for four consecutive days. It has been found to be of some value in generalized disease to relieve itching, fever and massive mediastinal involvement when used in combination with radiation therapy. Only 22 patients in our series have been so treated. Hormones, such as the adrenal steroid hormones, cortisone, hydrocortisone, metacorten, prednisone, prednisolone and the adrenocorticotropic hormone (ACTH), have been used only as adjunctive therapy in controlling hemolysis and promoting well-being but not as a specific or primary treatment for these patients.

LYMPHOSARCOMA AND RETICULUM CELL SARCOMA

ABSOLUTE SURVIVAL RATES

A long term analysis has been made of 402 patients with lymphosarcoma and reticulum cell sarcoma treated between 1922 and mid 1954. The five to thirty year absolute survival rates for these two conditions are presented in Table II. The abso-

TABLE II

LYMPHOSARCOMA AND RETICULUM CELL SARCOMA
ABSOLUTE SURVIVALS

(1922–mid 1954)

Survival Years	Total No. of Cases	No. of Survivals	Per Cent
30	39	2	5.2
25	78	5	6.4
20	133	15	11.2
15	191	24	12.5
10	280	56	20
5	402	107	26.5

lute five year survival rate for the entire group amounted to 26.5 per cent. This is 8 per cent less than that reported from Harper Hospital[5] for Hodgkin's disease during approximately the same period. It is of interest to note that the ten year survival rate of 280 patients was 20 per cent and that there are 2 patients in the series who have survived over thirty years. Of additional interest, although not shown in Table II, is the subclassification we made of male and female patients. As has been frequently noted, these malignancies affect a higher percentage of males. The survival rates among our female patients are significantly higher five, ten, fifteen, and twenty years after treatment than they are in the male group.

There are several series reported in the literature,[5,7,21,22,29,31,32,36] some of which are tabulated in Table III. This shows similar long term results in the treatment of malignant lymphomas. Because of differences in classification, selection of cases, method of follow-up and types of treatment, these series are not directly comparable.

FIVE YEAR SURVIVAL RATES

As already stated, the absolute five year survival rate for the entire series of lymphosarcoma and reticulum cell sarcoma amounted to 26.5 per cent. Table IV gives the five year survivals according to the stage of the disease. There is very little difference between the survival rates for males and females in Stages I and II reticulum cell sarcoma and Stage I lymphosarcoma. However, of those falling into the category of Stage II lymphosarcoma, nearly 32 per cent of the females survived five years and only 13 per cent of the males.

This table also demonstrates the more favorable results in lymphosarcoma than in reticulum cell sarcoma and, as expected, a significant difference in the five year survivals between those with relatively localized and those with generalized disease when first treated. Staging has been found to be more helpful in prognosis than in grading in the lymphoma group.[14,22,32]

Table V gives the five year survival rates of patients with lymphosarcoma and reticulum cell sarcoma in Stages I and II, chronologically divided into three periods: 1922–1934, 1935–1944, and 1945–1954. As may be noted, there has been a slight increase in the absolute survival rate for

TABLE III

COMPARATIVE LONG TERM RESULTS IN THE TREATMENT OF MALIGNANT LYMPHOMAS

Authors	Year	Five Year Survivals		Ten Year Survivals	
		No. of Cases	Per cent	No. of Cases	Per cent
Craver[7]	1947	308	26.3		
Stout[36]	1947	119	23.5		13.4
Hare, Mulry, and Sornberger[22]	1948	181	28.7		
Hamann[21]	1948	43	12		
Lenz, Wells, and Stout[29]	1950	242	27	172	17
Nice, and Stenstrom[31]	1951	132	18.9		
Nichols, Phillips, and Sommer[32]	1957	71	25.5	43	14
Cook, Krabbenhoft, and Leucutia	1959	402	26.5	280	20

TABLE IV

LYMPHOSARCOMA AND RETICULUM CELL SARCOMA
FIVE YEAR SURVIVALS RELATED TO STAGE OF DISEASE (1922–mid 1954)

	Total No. of Cases	Lymphosarcoma			Reticulum Cell Sarcoma		
		No. Treated	Five Year Survivals		No. Treated	Five Year Survivals	
			No.	Per cent		No.	Per cent
Stage I							
Male	149	109	39	35.7	40	9	22.2
Female	88	66	22	33.3	22	5	22.7
	237	175	61	34.8	62	14	22.5
Stage II							
Male	106	86	11	12.8	20	4	20
Female	59	47	15	31.9	12	2	16.6
	165	133	26	19.5	32	6	18.7
Total	402	308	87	28.2	94	20	21.2

both stages in those patients treated more recently. It is particularly gratifying to see a higher proportion of Stage I cases referred for treatment from 1945 to 1954 than in the period from 1935 to 1944.

Table VI presents the five year survival rates according to age distribution. This table emphasizes the relatively better prognosis in the age group between 20 and 50 years, the absolute survival being 40.1 per cent for this group as compared to 24.3 per cent for those patients under 20, and 16.6 per cent for those over 50 years of age. This better prognosis for the group referred for treatment between the ages of 20 and 50 was essentially in the same proportion for lymphosarcoma and reticulum cell sarcoma. The average age for the entire group was 41.5 years which is similar to that reported by other investigators. The sex of the patients, although not shown in this table, had no influence on the prognosis according to age distribution. The poor prognosis in the younger and older age groups is striking, and we believe is statistically significant.

STUDY OF PATIENTS WHO EXPIRED

To gain additional information about the value of radiation therapy in lymphosarcoma and reticulum cell sarcoma, a statistical analysis was performed also of those patients who expired.

Table VII gives the percentage of male and female patients with lymphosarcoma

TABLE V

LYMPHOSARCOMA AND RETICULUM CELL SARCOMA
FIVE YEAR SURVIVALS RELATED TO STAGE OF DISEASE AND PERIOD OF INITIAL TREATMENT
(1922–mid 1954)

Period of Initial Treatment	Stage of Disease	Total No. of Cases	Five Year Survivals	
			No.	Per Cent
1922–1934	I	47	14	29.7
	II	31	4	12.9
	Total	78	18	23
1935–1944	I	60	18	30
	II	53	10	18.8
	Total	113	28	24.7
1945–1954	I	127	42	33
	II	84	19	22.6
	Total	211	61	28.9

TABLE VI

LYMPHOSARCOMA AND RETICULUM CELL SARCOMA
FIVE YEAR SURVIVALS RELATED TO AGE DISTRIBUTION IN DECADES (1922–mid 1954)

Decade	Total No. of Cases	Five Year Survivals		Summary		
		No. of Cases	Per Cent	No. of Cases	Five Year Survivals	Per Cent
0–10	16	3	18.7			
11–20	25	7	28	41	10	24.3
21–30	33	15	45.4			
31–40	52	21	40.3			
41–50	72	27	37.5	157	63	40.1
51–60	101	19	18.8			
61–70	79	13	17.7			
71–80	22	2	9			
81–90	2			204	34	16.6
Total	402	107	26.5			

and reticulum cell sarcoma who expired during the first year, and includes the period 1922 to mid 1958. These figures are also useful in making a comparison with other reported series[33] as they suggest even more clearly than clinical staging the seriousness of the patients' condition when reporting for treatment. Of the entire group of 459 patients, 42.2 per cent did not live one year after the first treatment. This percentage is higher for the 114 cases of reticulum cell sarcoma (54.3 per cent) than for the 345 cases of lymphosarcoma (38.5 per cent). It may also be noted that the chances for a female patient to survive the first year are better than for the male patient in each pathologic division.

TABLE VII

LYMPHOSARCOMA AND RETICULUM CELL SARCOMA
PATIENTS WHO EXPIRED WITHIN ONE
YEAR AFTER REFERRAL
(1922–mid 1958)

Sex	No. Treated	Expired First Year	
		No. of Cases	Per Cent
	Lymphosarcoma		
Male	220	96	43.6
Female	125	36	28.8
Total	345	132	38.5
	Reticulm Cell Sarcoma		
Male	71	43	60.5
Female	43	19	44.1
Total	114	62	54.3
Combined Total	459	194	42.2

Table VIII gives the average survival in months according to sex for all patients with lymphosarcoma and reticulum cell sarcoma who expired during the period 1922 through mid 1958. In the lymphosarcoma group the female patients' average survival was 35.8 months as compared to 29.3 months for the male patients. In the reticulum cell sarcoma group the female patients have survived for an average of 21.1 months as compared to 17.5 months for the male patients. Obviously, these figures are only of relative value as they do not include those patients still living. If all of the patients could be followed to death, the average survival would be much longer. Of the 459 patients upon which these figures are based, 83.2 per cent have expired.

In an attempt to further evaluate the

TABLE VIII

LYMPHOSARCOMA AND RETICULUM CELL SARCOMA
AVERAGE SURVIVAL OF EXPIRED PATIENTS
(1922–mid 1958)

Sex	No. Expired	Average Survival (mo.)	No. Expired	Average Survival First Five Years (mo.)
	Lymphosarcoma			
Male	184	29.3	144	14.6
Female	101	35.8	76	21.4
	Reticulum Cell Sarcoma			
Male	59	17.5	47	11
Female	38	21.1	27	14.1

prognosis in this group, the average survival was calculated also for those patients who expired within the first five years after referral. The figures include 402 patients treated between 1922 and mid 1954 and are likewise presented in Table VIII. In lymphosarcoma the average survival of the female patients was 21.4 months as compared to 14.6 months for the male patients. In reticulum cell sarcoma the female patients had an average survival of 14.1 months and the male patients of 11 months. As was to be expected, the prognosis was distinctly better in lymphosarcoma than in reticulum cell sarcoma. Again, the average survival of the female patients was longer than that of the male patients in both categories. This longer average survival of the female patients, as shown in Tables VII and VIII, indicates a more chronic type of disease or, less probably, a better response to roentgen therapy in this sex.

GIANT FOLLICULAR LYMPHOMA

The giant follicular lymphoma is similar in many respects to the lymphosarcoma and reticulum cell sarcoma. Because of the better prognosis[40] and more favorable response to treatment, it was decided to separate it statistically from the other two conditions. Table IX is a statistical evaluation of this group. We have observed 55

TABLE IX

GIANT FOLLICULAR LYMPHOMA
STATISTICAL EVALUATION OF 55 PATIENTS (31 MALES—24 FEMALES)

	1936–Mid 1954			
Total No. of Cases	Five Year Survivals		Average Survival (expired during first five years)	
	No.	Per Cent	No.	Months
43	21	48.8	22	19.8

Age Distribution			
Decade	No.	Per Cent	Average Age
20–50	14	66.6	41.5 years
Others	7	31.8	

	1936–Mid 1958			
	Expired First Year		Average Survival (expired)	
	No.	Per Cent	Per Cent	Months
55	11	20	61.8	29.2

cases with an absolute five year survival rate, based on 43 cases presenting themselves for treatment between 1936 and mid 1954, of 48.8 per cent. This compares with the five year survival of 43.8 per cent of 16 cases reported by Stout,[36] 41 per cent of 43 cases reported by Lenz *et al.*[29] and 53 per cent of 42 cases by Gall *et al.*[16] As with the other entities, the males outnumber the females, there being 31 and 24 cases respectively. In this relatively small group of cases, there was no significant difference in the five year survival rate of males and females. The average age at the time of referral was 41.5 years. Gall *et al.*[16] gave an average age of 50 years. The range for our patients was from 17 weeks to 71 years, the best prognosis being in the group between 20 and 50 years of age. Only 20 per cent of the patients expired in the first year of treatment and the average survival was 29.2 months. The average survival for those patients expiring within the first five years after referral was 19.8 months.

SUMMARY

A series of 514 cases of lymphosarcoma, reticulum cell sarcoma and giant follicular lymphoma treated by roentgen therapy at Harper Hospital from 1922 through mid 1958 is presented. Although individual consideration of treatment is essential in producing increased results, a treatment plan is presented which can be adapted to most cases. This entails rapid and massive treatment of large areas of the body for what can be considered a systemic disease. Lower total tumor doses are used and judicious repetition of treatment is advocated. This plan, together with careful adjunctive therapy, and frequent and prolonged observation of each individual patient can lead to good remission and palliation comparable to that achieved by other methods. Chemotherapy was found to have only slight palliative value.

Detailed analysis of this series is made, considering the location of the primary site related to the pathologic entity, the stage of disease at the time of referral, the sex and the age. Where figures are statistically significant, the data are related to survival.

The 459 cases of lymphosarcoma and reticulum cell sarcoma are presented in five year groups from five years to thirty years, the absolute five year survival rate for the two groups being 26.5 per cent. Further analysis of patients expiring in the first five years reveals a preponderance of male patients and a better prognosis for the female patient, not only in absolute results but also in average monthly survival of expired patients. As has been previously noted by many investigators, the extent of disease at the time of referral is of primary importance in survival. Patients with reticulum cell sarcoma have a poorer radiation and survival response than patients with lymphosarcoma who, in turn, have a poorer response than patients with giant follicular lymphoma.

Fifty-five cases of giant follicular lymphoma are dealt with separately because of the known better prognosis in this lesion.

The best prognosis in all three entities was in the group which contracted the disease between the ages of 20 and 50 years.

James C. Cook, M.D.
Harper Hospital
Detroit 1, Michigan

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LYMPH NODE SCINTIGRAMS*

By HAROLD H. SAGE, M.D.,† DOGAN KIZILAY, M.D.,‡ MAKOTO MIYAZAKI, M.D.,‡ GERALD SHAPIRO,§ *and* BIRENDRA SINHA, M.D.‡

NEW YORK, NEW YORK

LYMPH node scintigrams, radioisotope patterns of lymph node drainage, which were originally obtained in dogs,[1] have now been obtained in the upper and lower extremities and the head and neck regions of intact humans. Colloidal Au^{198} injected into tissues is carried through lymphatic pathways to regional draining lymph nodes.

The various sites of deposition and concentration of the isotope in the lymph nodes are recorded by means of a moving scintillation counter. The graphic pattern of the scan depends on the sensitivity of the crystal and the kinetics of the scintiscanner. The scanner moves automatically across and down the field to be investigated, at a speed and spacing which can be varied to aid in the delineation of lymph nodes as compared with background. A scan of the inguinal or axillary region or neck may require thirty to sixty minutes. The pattern also depends on the size and type of crystal used as well as the collimator opening and the focusing devices. The technical factors of importance include the use of a pulse height analyzer and calculated base and window conditions, the use of a cone and the proper distance of the crystal from the source. The closer the crystal to the source of activity, the better the delineation.

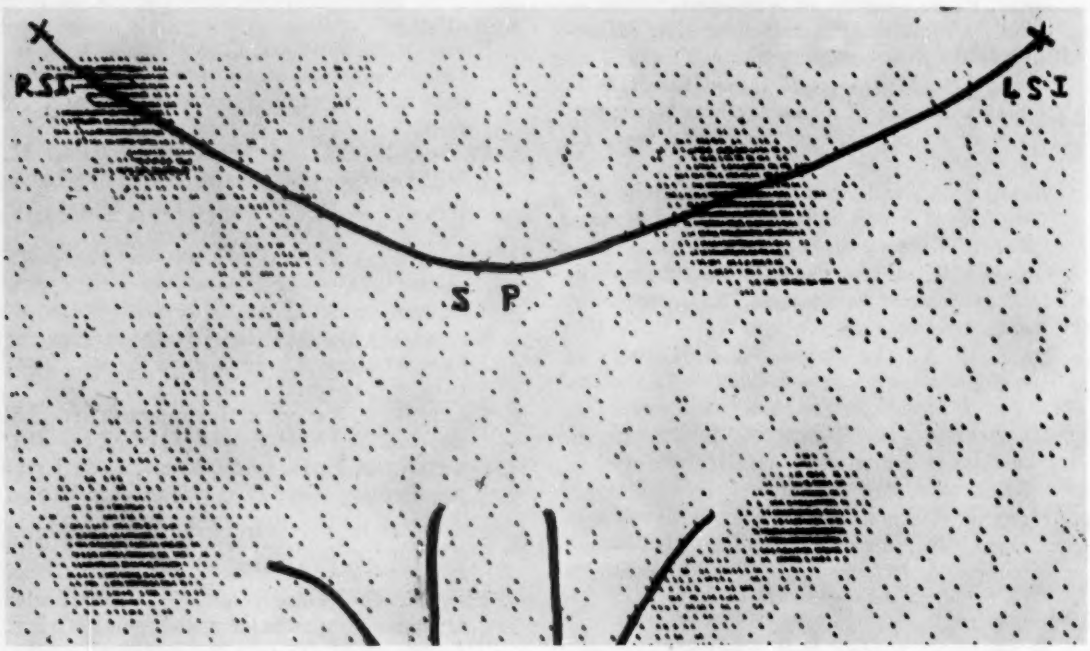

FIG. 1. A bilateral simultaneous anteroposterior scan of the groin after an injection into the dorsum of both feet. The femoral lymph nodes are generally definable in six to twelve hours and the inguinal lymph nodes in twenty-four to forty-eight hours.

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† Cancer Coordinator and Assistant Professor of Surgery, New York University College of Medicine; and Research Advisor, Guggenheim Institute, New York University College of Dentistry.

‡ Research Fellows, Guggenheim Institute, New York University College of Dentistry.

§ Physicist.

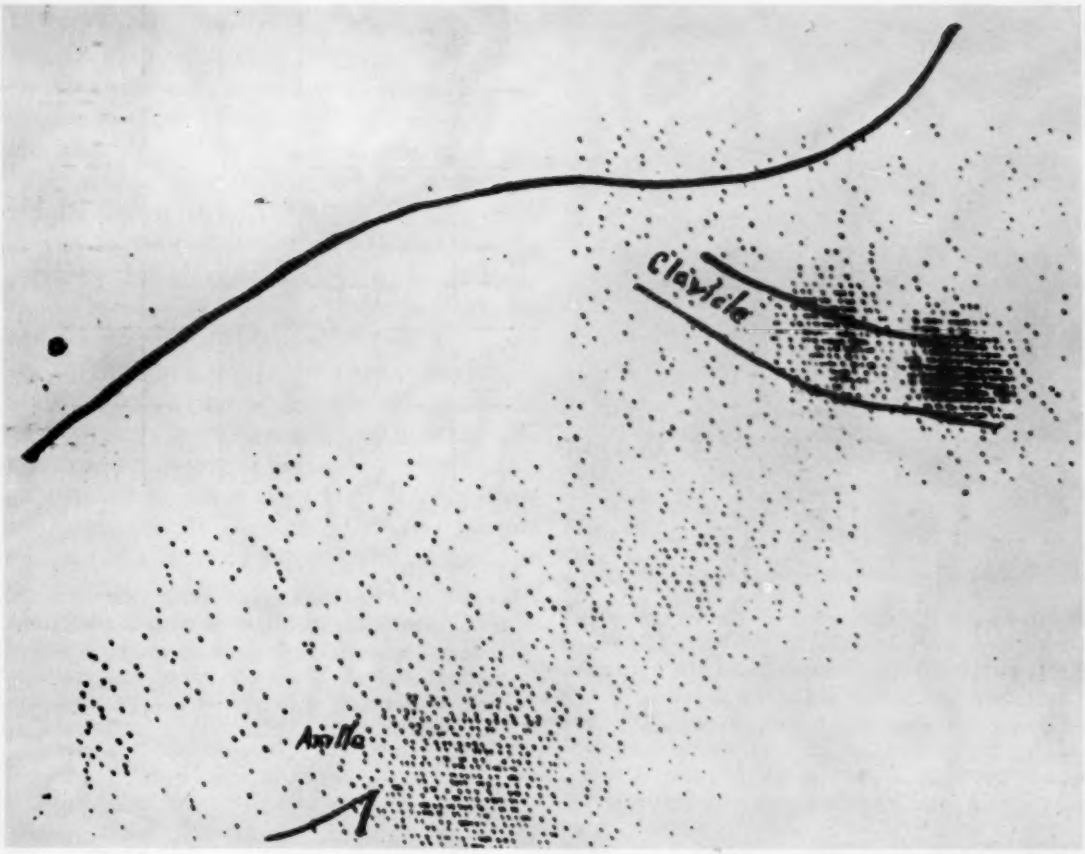

Fig. 2. A normal axillary scan after injection of the volar surface of the lower forearm. The axillary lymph nodes show up first and the supraclavicular lymph nodes later.

The factors which influence the dynamics, quantity and pattern of pickup include the isotope used, its particle size, and the volume and pressure of the injected material. Baseline conditions generally used were 0.1 cc. liquid containing 50 to 100 μc of Au^{198} of 0.003 μ average size. An electron microscope is employed to photograph the various particle sizes. Pickup also depends on the tissue injected and the plane of injection since the skin, subcutaneous tissue, muscle and other tissues vary in the capacity and pattern of their lymphatic drainage.

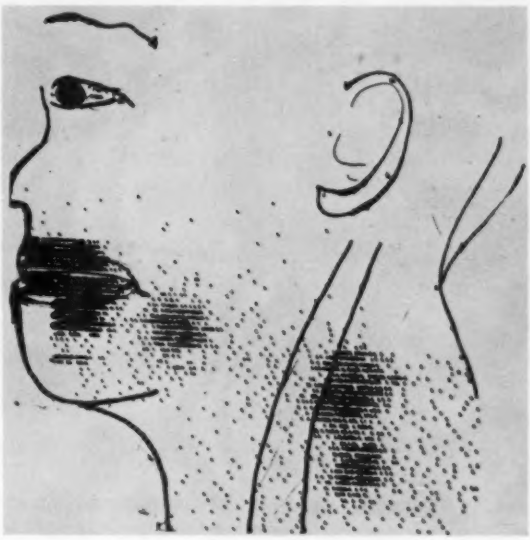

Fig. 3. A normal lateral neck scan after injection of the lip on one side. The submaxillary lymph nodes are a superficial chain which appear first when the lip is injected and the upper and lower jugular lymph nodes appear later.

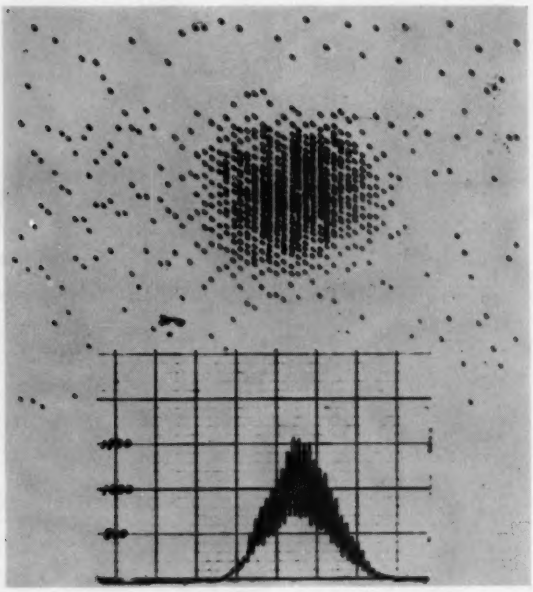

FIG. 4. An anteroposterior scan of the femoral lymph node area after injection of the foot. The count rate meter when run simultaneously helps quantitate the concentration in the lymph nodes.

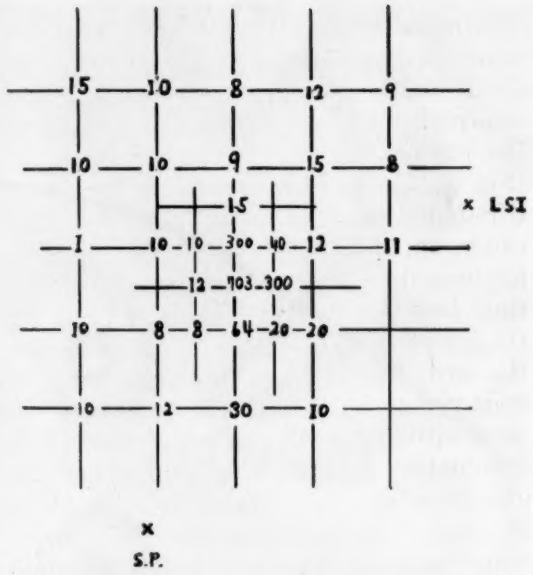

FIG. 5. Grid count over lymph node area. Note the obvious difference in the count over the lymph node as compared with the surrounding area and the quick fall-off. This makes lymph node scanning more satisfactory than similar isotope studies in other organs.

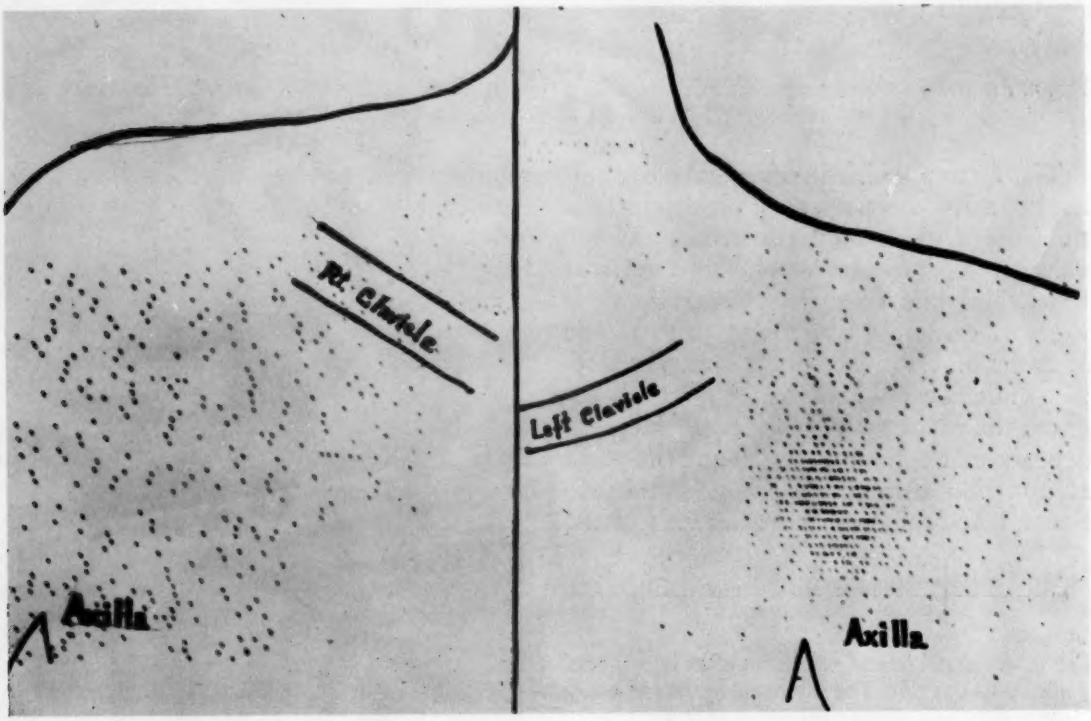

FIG. 6. A case of extensive melanoma of the right arm with axillary and supraclavicular lymph node metastases. Compare the absent lymph node pickup with the opposite side.

Lymphatic scintigrams have been obtained without difficulty several hundred times and in most respects are easier to interpret than comparable scintigrams of the thyroid, liver, bone marrow or brain (Fig. 1, 2, 3 and 4). The lymph nodes are situated close to the skin, thus the crystal can be applied at a relatively short distance for finer delineation of areas of concentration. Because of the superficial location of the lymph nodes, there is little scatter from the surrounding structures. Also, the lymph node pickup is of a high order of magnitude as compared with background, making discrimination easier. This is well seen in the grid quantitation studies (Fig. 5), showing the high counts directly over the lymph nodes and the rapid fall-off. Concentration of the Au^{198} in lymph nodes is detectable with a scan at twice the background. Within six to twenty-four hours after injection, the concentration in lymph nodes may reach several hundred times this amount.

Various physiologic factors influence lymphatic flow and lymph node pickup. Exercise and muscle action speed up the flow and increase the pickup markedly. Hyaluronidase increases the pickup. Mechanical massage or the use of a mechanical milking device also speeds up the lymph flow and pickup.[2]

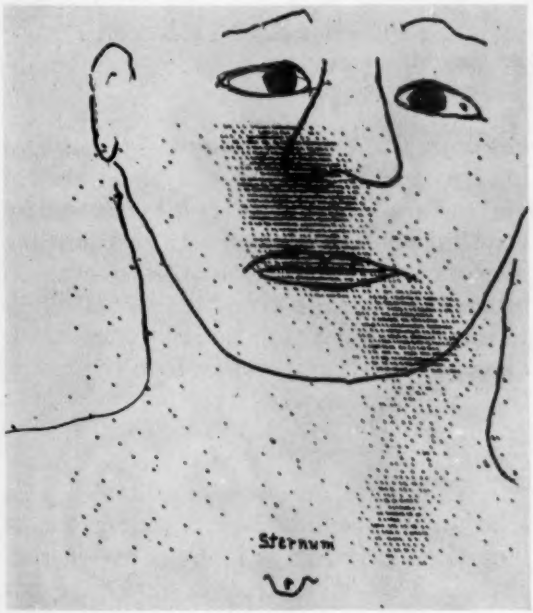

Fig. 7. Absent pickup in the right neck lymph nodes after right radical neck dissection. Left side normal. The midline of the tongue was injected and an anteroposterior cervical scintiscan made.

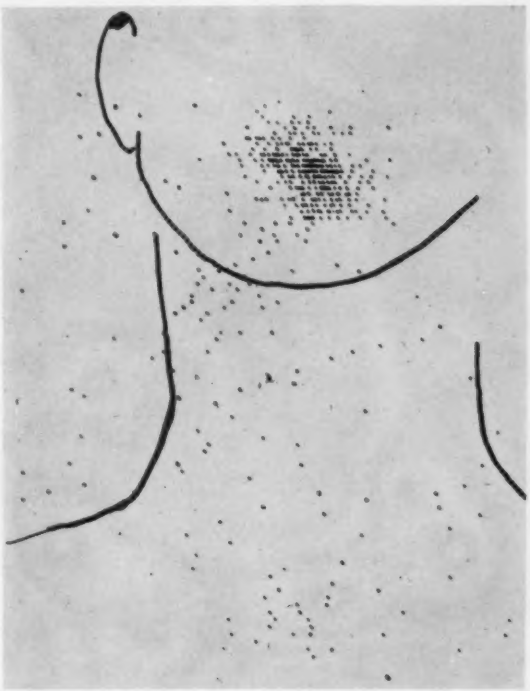

Fig. 8. No lymph node pickup on either side in an anteroposterior cervical scintiscan. The tongue was injected in the midline. This patient had a bilateral radical neck dissection.

There are several advantages of this technique compared with others used for demonstrating anatomic, functional and pathologic pathways of lymphatic drainage. It permits serial or continuous observations of lymph node pickup over a period of at least seven days since the half life of Au^{198} is 2.69 days. It also minimizes the problems of excess volume and pressure phenomena which attend injection of contrast material or the use of radiopaque agents. There is no alteration of the physiologic or functional pathways by operative exposure. Thus, observations need not be limited to a single point or time and conditions may be altered during the course of the study. Secondary and variable routes of lymph node drainage are demonstrable.

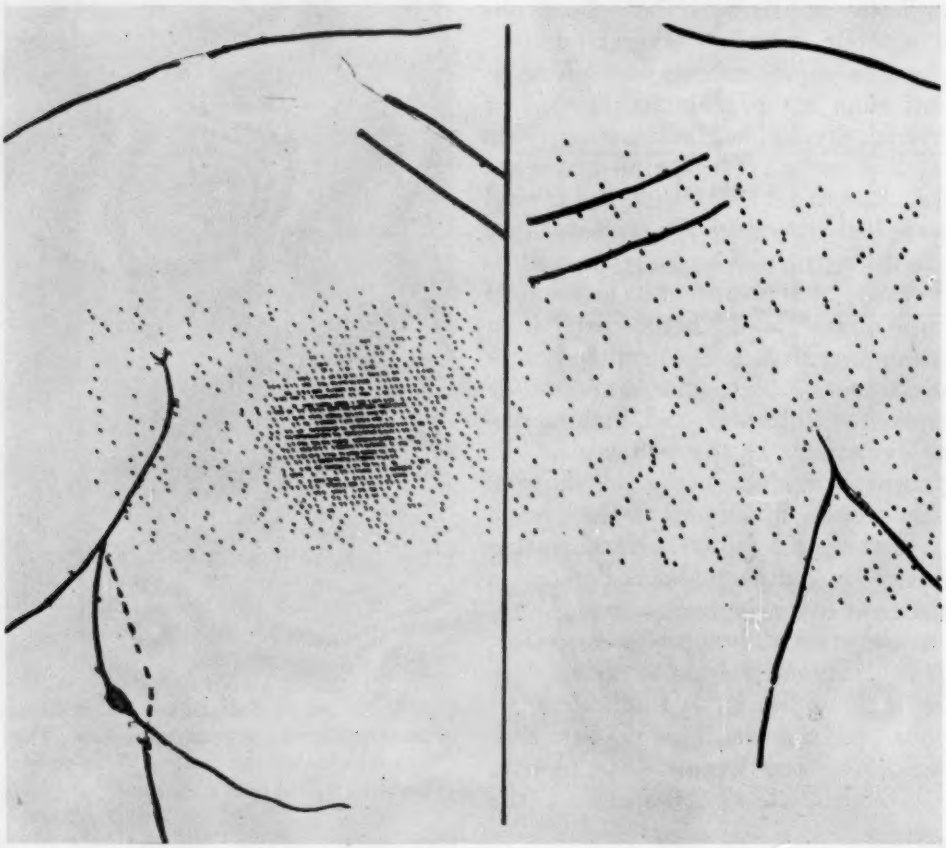

FIG. 9. Anteroposterior axillary scintigram showing absent axillary lymph node pickup after radical mastectomy. Compare with the normal opposite side.

Various pathologic conditions of importance alter the normal pattern of lymph node pickup. Alterations from normal lymphatic and lymph node pickup are shown in cases with cancer deposition in lymph nodes, operative excision of lymph nodes, surgical scar and radiation therapy (Fig. 6, 7, 8, 9, 10, 11 and 12).

Lymph node scanning is one of several radioisotope techniques devised to study the intact lymphatic circulation as well as lymph node pickup function. The pickup in lymph nodes is measured quantitatively[3] by continuous or intermittent serial counts of the gamma radiation emitted by Au^{198}.

Lymphatic circulation is also measured by disappearance rates from the site of injection. Bypassing of lymph nodes by the circulating lymph occurs under various normal and pathologic conditions. This unfiltered lymph enters the blood stream via the thoracic duct. It is measured by counting the deposition of Au^{198} in the liver and spleen. Thus, quantitative measurements are made over these areas simultaneously with lymph node studies to indicate the percentage of isotope bypassing the lymph nodes.

SUMMARY

A technique of obtaining lymph node scintigrams—radioisotope patterns of lymph node drainage in humans—is presented. This is one of several methods utilizing radioactive colloidal gold which have been devised for demonstrating the functional patterns, dynamics and quantitative particle pickup by intact lymphatics

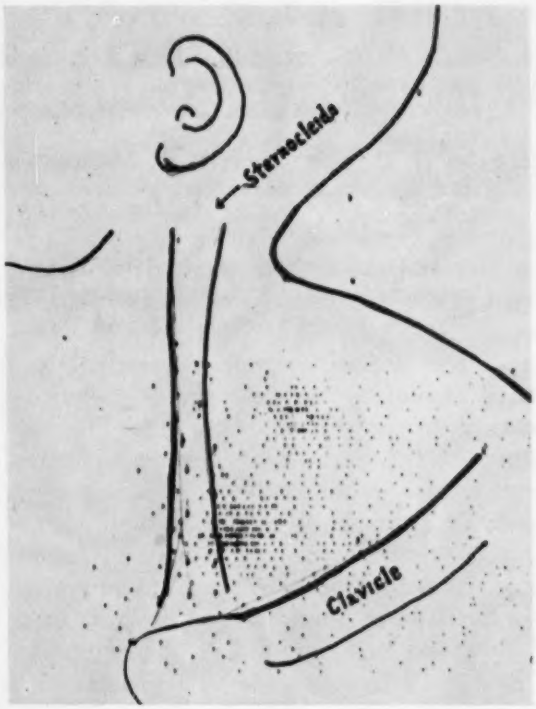

FIG. 10. Absent axillary lymph node pickup after radical mastectomy but pickup is present in two lymph node areas in the supraclavicular space.

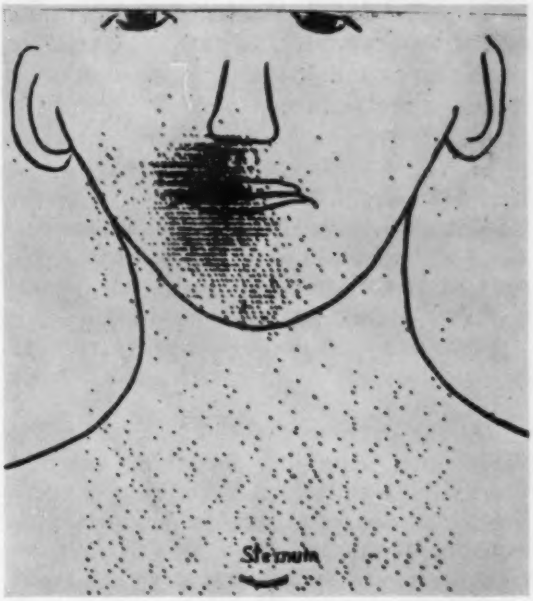

FIG. 11. Absent pickup in neck lymph nodes after intensive radiation therapy. Tongue injected.

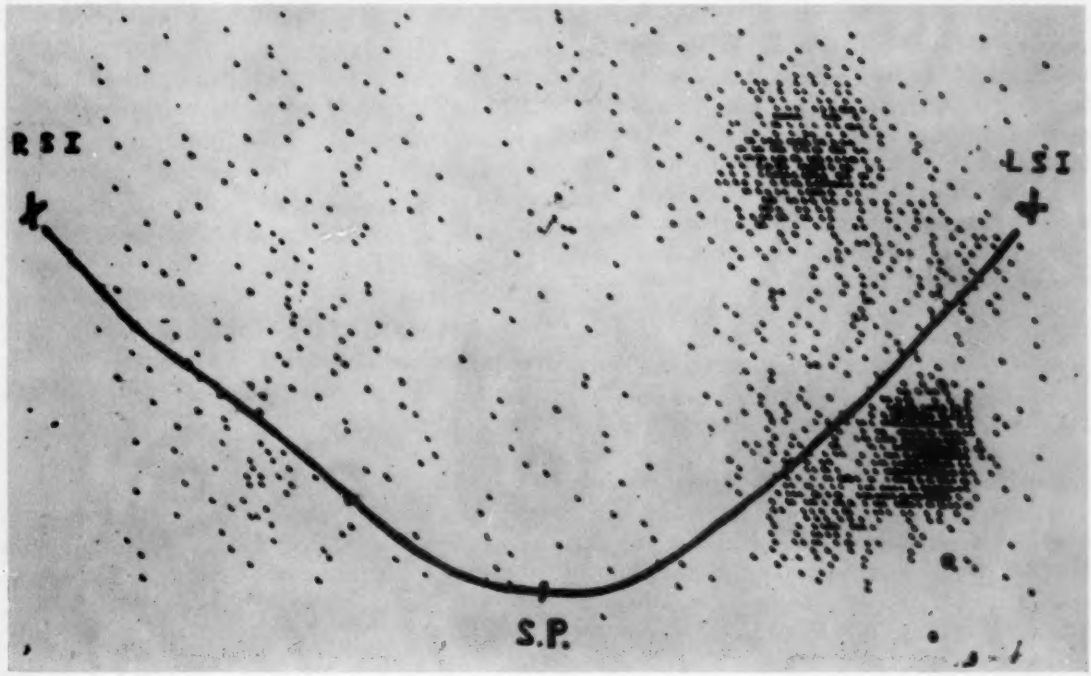

FIG. 12. Anteroposterior scintigram showing poor pickup in the right groin lymph nodes in a patient with cancer of the uterus who had intensive pelvic irradiation. This may be due to the disease as well as treatment.

and lymph nodes serially and without operative exposure. Normal anatomic, physiologic and pathologic pathways of drainage are shown.

Harold H. Sage, M.D.
New York University—Bellevue Medical Center
New York University College of Medicine
550 First Avenue
New York 16, New York

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RESPONSE OF PULMONARY AND SOFT TISSUE METASTASES FROM CARCINOMA OF THE THYROID TO RADIOACTIVE IODINE THERAPY*

By SIMON KRAMER, M.D.,† *and* JOSEPH P. CONCANNON, M.D.‡
PHILADELPHIA, PENNSYLVANIA

SEVERAL reports[1,2,4,6,7,10] have appeared in the literature describing regression or disappearance of pulmonary metastases from thyroid cancer following radioactive iodine therapy. Some of the patients reported have survived for prolonged periods of time without clinical or roentgenologic evidence of disease. It is our impression that the chance for prolonged survival following radioiodine therapy is better when the cancer has spread only to the lymph nodes and the lungs, and that there is less prospect of obtaining complete clinical regression of the disease once bone metastases are present.

We have observed 4 patients who concentrated radioiodine in pulmonary metastases from thyroid cancer. The case histories of these patients and the response of their disease to I^{131} therapy form the basis of this report.

In the previous paper[5] reporting a series of patients with thyroid cancer investigated or treated with radioactive iodine we stated, "ablation of the thyroid was not successful in increasing iodine uptake in those patients who had no evidence of iodine concentration in the tumor at the time of the initial tracer study." It is interesting to note that 3 of the patients reported in this communication concentrated radioiodine in tumor tissue only after ablation of the thyroid.

REPORT OF CASES

CASE 1. M.S. This patient of Professor D. W. Smithers has been previously reported by Walton,[11] Smithers,[8,9] and by us.[5] She was a young woman twenty years of age in June, 1948, when she first complained of respiratory symptoms, thyroid enlargement, hoarseness and loss of voice. Since she refused surgery, she was placed on thiouracil. Increased symptoms in December, 1948 necessitated surgery; however, only the isthmus of the thyroid was divided and removed, and tracheotomy was done.

The patient was admitted to the Royal Cancer Hospital in April, 1949. The thyroid was enlarged and fixed, with several small, hard, mobile lymph nodes present in the posterior cervical triangles and one lymph node in the left supraclavicular fossa. Laryngoscopy showed bilateral abductor paralysis of the cords. A roentgenogram (Fig. 1) showed miliary infiltration in the lungs compatible with a diagnosis of hematogenous carcinoma. A posterior cervical lymph node was removed for biopsy shortly after admission and showed a well differentiated alveolar adenocarcinoma with considerable colloid and infrequent mitoses..

Tracer studies indicated that there was concentration of radioiodine, both in the lungs and the thyroid gland. The patient was given 50 mc of I^{131} in April, 1949, 88 mc in May, 1949, 100 mc in August, 1949, 230 mc in December, 1949 and 160 mc in August, 1950. The total amount administered was 628 mc over a period of sixteen months. A posterior cervical lymph node was removed in December, 1949, following a tracer dose of iodine, and, although showing anaplastic carcinoma with no colloid, it had a high iodine content on physical assay.

There was some relief of symptoms following the first therapeutic administration of I^{131} and following the second therapeutic drink the previously fixed left vocal cord began to move. The tracheotomy was allowed to close. After the third course of I^{131}, the patient no longer complained of troublesome symptoms other than those referable to the myxedematous state. Although there was a continuous de-

* From the Jefferson Medical Center, Philadelphia, Pennsylvania.
† Professor of Radiology, Jefferson Medical College, Philadelphia, Pennsylvania.
‡ Radiation Therapist, The Allegheny General Hospital, Pittsburgh, Pennsylvania.

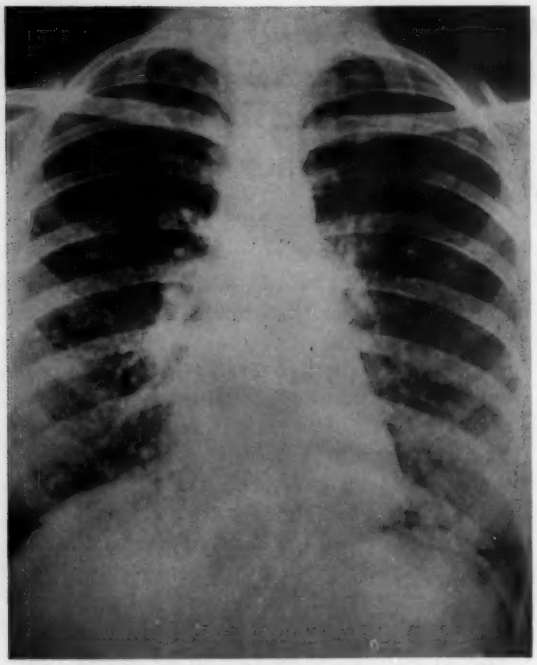

Fig. 1. Case 1. Roentgenogram of the chest in December, 1948 shows extensive infiltrative lesions in the pulmonary parenchyma.

crease in the size of the thyroid mass and decrease in the degree of compression of the trachea, chest roentgenograms showed no appreciable alteration until May, 1950, when it was thought that the nodular appearance of the lungs was less marked. By June, 1951 the pulmonary parenchyma was clear and no evidence of metastatic disease could be seen. Additional diagnostic studies in May and June, 1951 showed slight uptake in the neck and none in the chest.

The patient was last heard of in March, 1958, when no evidence of residual tumor could be detected. A chest roentgenogram taken in February, 1957 was negative (Fig. 2). She was married in 1954; she has a normal three year old child and is expecting another baby.

Comment. This patient almost certainly would have died of her disease if it had not been for the use of radioactive iodine. She is alive without evidence of disease nine years after the first therapeutic drink of radioactive iodine. The primary and metastatic lesions in the neck and lungs acquired radioiodine in an appreciable quantity even in the presence of normal thyroid tissue. It is noteworthy that a lymph node still contained radioiodine although it was replaced by anaplastic carcinoma.

Case II. J.McK. This patient of Dr. Paschkis was first seen at Jefferson Hospital in April, 1949. She then had a two year history of an enlarging mass in the right side of her neck and had pain in her chest, cough and weight loss for one year. Physical examination in April, 1949 revealed a mass in the right lobe of the thyroid and enlarged right cervical lymph nodes. Her general condition was deteriorating rapidly. A roentgenogram of the chest showed widespread infiltrative lesions in the pulmonary parenchyma compatible with metastatic disease (Fig. 3). She was seen at that time by Dr. Eberhard, who subsequently was responsible for all the roentgen-ray and radioiodine therapy. A scan performed after a diagnostic quantity of I^{131} had been administered showed no evidence of concentration of the iodine in the pulmonary lesions.

Total thyroidectomy and right radical neck dissection were done in May, 1949, but residual cancer was left behind in the neck. Histologic examination showed the tumor to be a papillary adenocarcinoma. The patient was then treated by external radiation therapy to the neck. Two lateral portals 6 by 8 cm. were used and 3,000 r

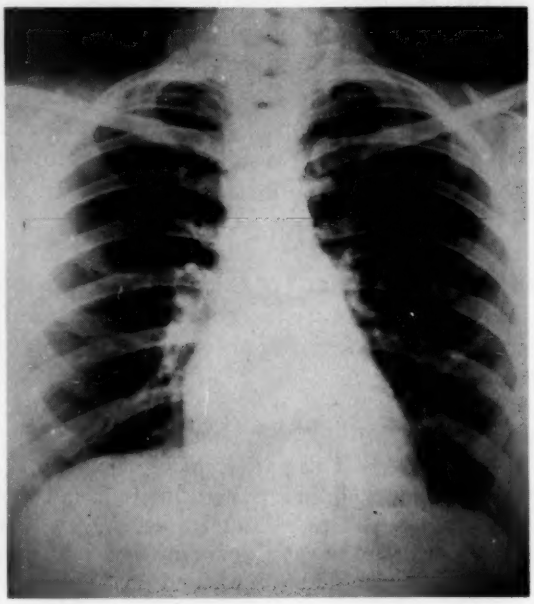

Fig. 2. Case 1. Roentgenogram of the chest in February, 1957 shows no abnormalities in the lung fields.

in air was given to each portal with an estimated tumor dose of 3,000 r in the midplane of the neck. The radiation was given between May 3, 1949 and July 6, 1949 with a 200 kv. apparatus, filter 0.25 mm. Cu and 1.0 mm. Al, half value layer 1.0 mm. Cu, and a focus skin distance of 50 cm.

A repeat tracer study in July of 1949 showed definite concentration of radioiodine in the pulmonary tissue and 100 mc of I^{131} was given to the patient. A chest roentgenogram fifteen days later showed the appearance of a pleural effusion on the right which soon resolved. The patient was given 88 mc of I^{131} in September and 90 mc in November of 1949. She received 75 mc of I^{131} in April of 1952 in three divided doses. A final dose of 100 mc was given in March of 1954. Repeated scanning since that time has shown no concentration of radioactive iodine anywhere in the body.

Regression of the chest lesions was first noted on a roentgenogram in March of 1951. The pulmonary lesions had completely disappeared by October of 1955. The last roentgenogram in December of 1958 showed what appeared to be a perfectly normal chest (Fig. 4).

Fig. 4. Case II. Roentgenogram of the chest in December, 1958 shows what appears to be a normal chest.

Comment. The metastases in this patient showed evidence of function only after the thyroidectomy and roentgen-ray therapy to the neck. She also had one of the complications of radioiodine therapy for pulmonary metastases in that she developed a pleural effusion after the first therapeutic drink of radioactive iodine. She is alive without evidence of disease nine years after the first administration of I^{131}.

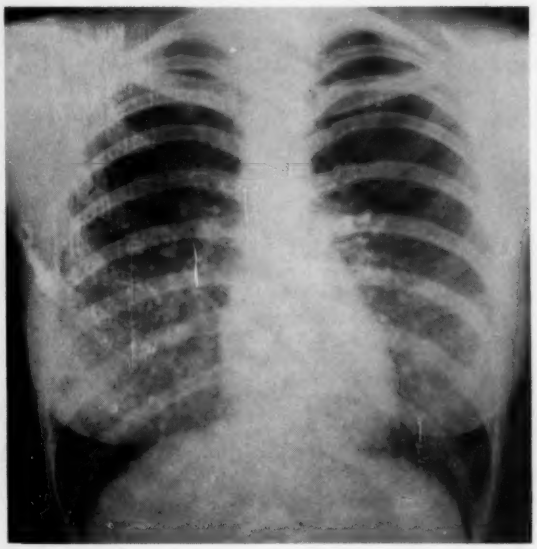

Fig. 3. Case II. Roentgenogram of the chest in 1949 shows bilateral pulmonary infiltration.

Case III. N.B. This was a twenty-one year old white male when he was first seen at Jefferson Hospital in September of 1956. In 1945 he had been seen at another hospital where a diagnosis of calcified tuberculous lymph nodes in the neck was made, although no biopsy was performed. A routine chest roentgenogram in September of 1956 showed miliary densities throughout the lung fields (Fig. 5). A biopsy of the lung was done at the Barton Division of the Jefferson Hospital and a histologic diagnosis of papillary and alveolar metastatic thyroid carcinoma was made. The patient was then transferred to Jefferson Hospital for further study and treatment.

On admission, there were several nodules in the enlarged right lobe of the thyroid gland and palpable lymph nodes in the right cervical chain. On October 29, 1956 the patient received 250 μc of I^{131}. There was a 30 per cent uptake in the thyroid. A scintiscan on October 30,

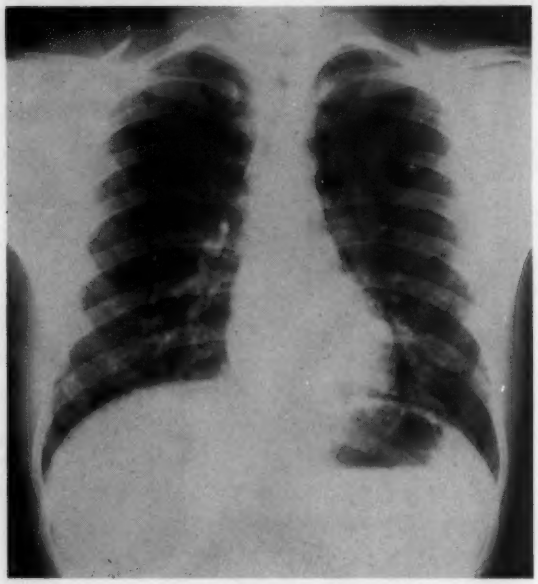

FIG. 5. Case III. Roentgenogram in September, 1956 shows fine, nodular, miliary lesions in the pulmonary parenchyma proved by biopsy to be mixed papillary and alveolar adenocarcinoma.

1956 demonstrated concentration of the radioiodine in the left lobe of the thyroid and markedly diminished radioactivity in the right lobe (Fig. 6). There was no evidence of uptake in the cervical lymph nodes or pulmonary metastases.

Exploration of the neck was done on November 13, 1956. The tumor in the right lobe of the thyroid had extended beyond the capsule of the gland and had invaded the sternomastoid muscle, the carotid sheath, and internal jugular vein. Posteriorly on the right the tumor extended behind the pharynx and was continuous with large nodular lymphatic masses. A left lobectomy with removal of the isthmus was done. A segment of the tumor where it had invaded the strap muscles was excised from the right side of the neck. The remainder of the tumor and the large lymph nodes were left untouched.

Two days postoperatively another dose of 250 μc of I^{131} was given and the uptake study showed that 31 per cent of the iodine given was localized in the neck. A scan at that time showed concentration of the radioiodine in the right lobe of the thyroid gland, but there was no evidence of iodine deposition in the lymph nodes or chest (Fig. 7).

The patient was given 70 mc of I^{131} by mouth on December 7, 1956. A scan in February, 1957 showed evidence of radioiodine concentration in the right lobe of the thyroid and in the cervical lymph nodes, but none in the chest.

Therapy was postponed in the hope that further delay would result in an increased percentage of the dose localizing in the neck. Repeat uptake and scan on April 25, 1957 (Fig. 8) showed the uptake in the neck to have increased from 14 to 30 per cent. He was given

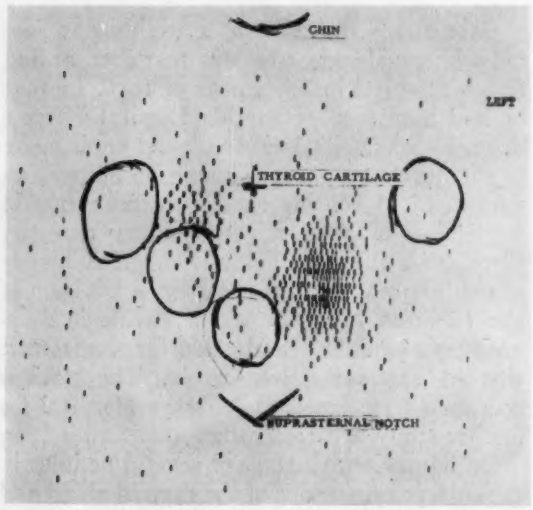

FIG. 6. Case III. Preoperative scintigram. The radioactivity is mainly in the normal left lobe of the thyroid gland. There is no activity in the nodular masses.

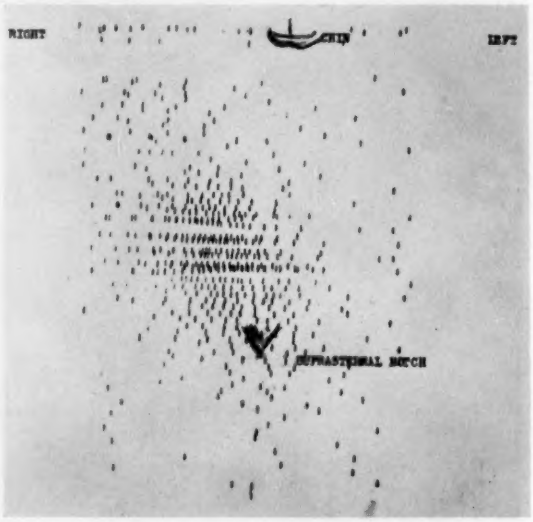

FIG. 7. Case III. Postoperative scintigram. The radioactivity is localized in the carcinomatous mass in the right lobe of the thyroid.

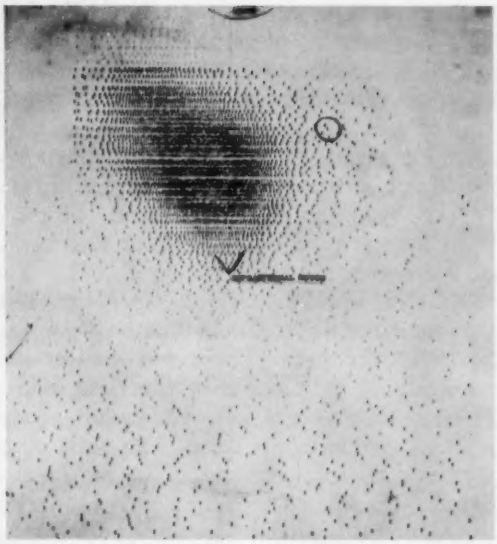

Fig. 8. Case III. Scintigram in April, 1957 shows evidence of radioactivity in the right lobe of the thyroid gland and in the right cervical metastatic lymph nodes.

108 mc of I^{131} in April of 1957.

Concentration of radioiodine in the pulmonary metastases was first observed after a tracer dose in August of 1957. Considerable radioactivity was again noted in the primary tumor and lymph nodes. The patient was then given 90 mg. of tapazole daily for one month. A tracer dose of 2 mc of I^{131} two days after cessation of tapazole therapy showed 40 per cent of the dose localized in his chest, as determined by profile scan measurements.[9] This represented a significant increase over the percentage uptake prior to tapazole therapy. The scintiscan of the neck and chest on September 20, 1957 is shown in Figure 9.

The patient was given a therapeutic quantity of 150 mc of radioactive iodine on September 27, 1957. Since that time repeated scanning has shown no evidence of I^{131} localization in the chest or neck. The large masses in the thyroid and in the cervical areas have now disappeared. There are still several small hard lymph nodes in the right cervical chain which on roentgenographic examination are seen to be calcified. A chest roentgenogram in October of 1958 showed almost complete clearing of the metastatic lesions (Fig. 10).

Comment. This is the only patient who had a biopsy of the lung lesions in the group reported here. The diagnosis in the other 3 patients was substantiated by the concentration of the radioiodine in the

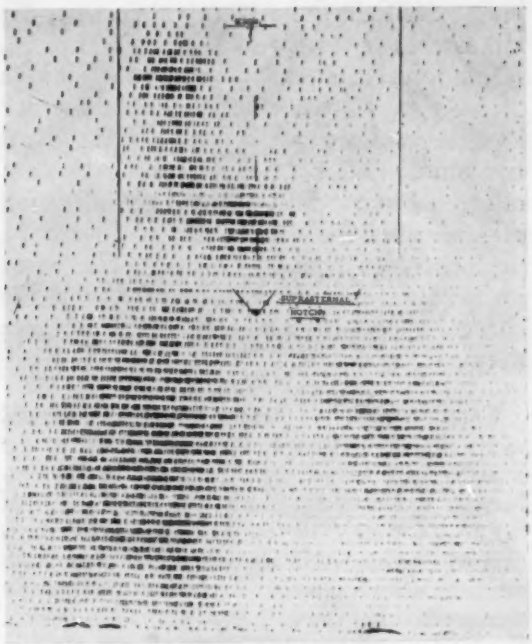

Fig. 9. Case III. Scintigram in September, 1957 shows evidence of radioiodine localization in the right lobe of the thyroid gland, in the cervical lymph nodes and in the pulmonary lesions.

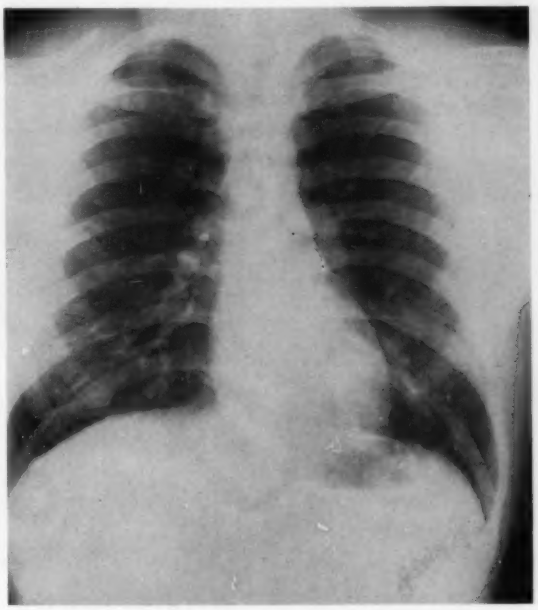

Fig. 10. Case III. Roentgenogram in October, 1958 shows almost complete clearing of the miliary lesions.

lungs. Neither the primary lesion nor its metastases concentrated radioiodine before surgical removal of the normal left lobe of the thyroid. Radioactive iodine did not localize in the cervical lymph nodes until two months after the first therapeutic dose of radioactive iodine. Selective localization of radioactivity in his chest could not be demonstrated until July of 1957. There was an increased percentage uptake of I^{131} in the chest lesions after a course of tapazole therapy.

Case iv. F.C. This was a seventeen year old white male when he was first admitted to the Ward Service of Jefferson Hospital in September, 1951. He had a mass in the right side of his neck for eight to ten years prior to admission to this hospital. The chest roentgenogram on admission showed extensive pulmonary changes compatible with metastatic carcinoma. Physical examination showed a large mass in the right lobe of the thyroid gland and large lymph node masses in the right cervical chain. Scanning at this time showed concentration of radioactive iodine in the neck, but none in the chest. A cervical lymph node biopsy was done on September 18, 1951 with a histologic diagnosis of alveolar adenocarcinoma.

The patient was then referred to Dr. Eberhard who administered the roentgen-ray and radioiodine therapy between that time and 1954. The patient was treated by external radiation therapy with four portals measuring 10 by 10 cm. Treatment was administered with a 200 kv. apparatus, filter 0.25 mm. Cu plus 1.0 mm. Al, half value layer 1.0 mm. Cu, and 50 cm. focus skin distance. He was given a total of 4,000 r in air to each field; the estimated tumor dose was 5,760 r. This treatment was carried out between October 3, 1951 and January 15, 1952. The patient received 100 mc of I^{131} in four divided doses between October 18 and November 8, 1951.

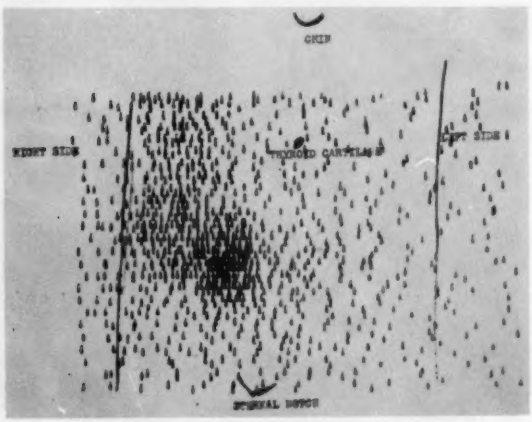

Fig. 11. Case iv. Scintigram in July, 1954 shows evidence of concentration of radioactive iodine in the right lobe of the thyroid and in the metastasis in the right cervical region.

An iodine uptake study and scan were done in January of 1952. There was a 7 per cent uptake in the neck. There was greater concentration of radioiodine in the right side of the neck than in the left. There was no evidence of uptake in the chest. The patient was given an additional 25 mc of iodine in March of 1952. He then failed to return until January of 1953. Uptake studies in January and October of 1953 showed 12 per cent of the dose localized in the neck on each of these occasions. On July 8, 1954 a dose of 250 μc of I^{131} was given. The uptake again was 12 per cent and scanning on July 9, 1954 revealed evidence of radioactivity in the right lobe of the thyroid and in the metastatic lymph nodes (Fig. 11). No evidence of radioactivity was discovered in the lungs.

The patient failed to return until July of 1956. On July 11, 1956 he was given 1 mc of I^{131}. The uptake in the neck at this time was 14 per cent and a scan on July 12, 1956 again demonstrated the presence of I^{131} in the cervical lymph nodes and the right lobe of the thyroid (Fig. 12). He was then given 50 mc of I^{131}. The patient was again lost to follow-up until December of 1958. Scintiscanning now showed evidence of concentration of I^{131} in the right lobe of the thyroid gland, in the metastatic areas in the right neck and, for the first time, in the pulmonary metastases (Fig. 13). Ten per cent of the diagnostic dose had localized in the chest and 1 per cent in the neck. The patient was given 200 mc of I^{131} in December of 1958. At this time there was a flat movable mass 4 cm. in width in the right lobe of the thyroid gland. There was some thickening in the right cervical region, but no discrete lymph nodes were palpable. A recent chest roentgenogram showed relatively little change in the appearance of the pulmonary metastases since 1951.

Comment. The management of this patient has been difficult because of his unwillingness to cooperate. His case also il-

lustrates the fact that radioiodine localization in the metastases may occur only after thyroid ablation. There was no detectable uptake in the pulmonary metastases as long as an appreciable quantity of the radioactive iodine localized in his neck. Had his cooperation been satisfactory and if radioactive iodine therapy had been more vigorous, it is quite likely that I^{131} concentration in pulmonary metastases could have been obtained earlier.

DISCUSSION

It is well known that patients with metastatic thyroid cancer may survive for long periods of time even when untreated. Case IV had extensive metastatic disease in his lungs in 1951 and was still alive and well in 1958 despite the presence of the pulmonary metastases. There had been no evidence of I^{131} concentration in these pulmonary metastases until recently and it is unlikely that the radioiodine therapy prior to December, 1958 had any effect on the pulmonary lesions. Case III had both local disease and pulmonary metastases treated by radioactive iodine only. This treatment has caused disappearance not only of the asymptomatic pulmonary lesions, but also of the masses in the neck, which were giving rise to pressure symptoms. Even so, we do not know how the disappearance of these lesions has altered his ultimate prognosis. We feel certain, however, that Case I owes her life to radioiodine therapy. She was cachectic and markedly ill when first seen. Her local disease was advanced beyond the possibility of control by any other method, yet she is alive, well and without evidence of disease nine years later. Case II had a total thyroidectomy and right radical neck dissection, with roentgen-ray therapy for the residual local disease. Surgery and roentgen-ray therapy may have controlled the local disease in her neck. Her general condition, however, was deteriorating rapidly, and there is little doubt that the radioactive iodine therapy has materially lengthened her life. The chest lesions have disappeared following this therapy.

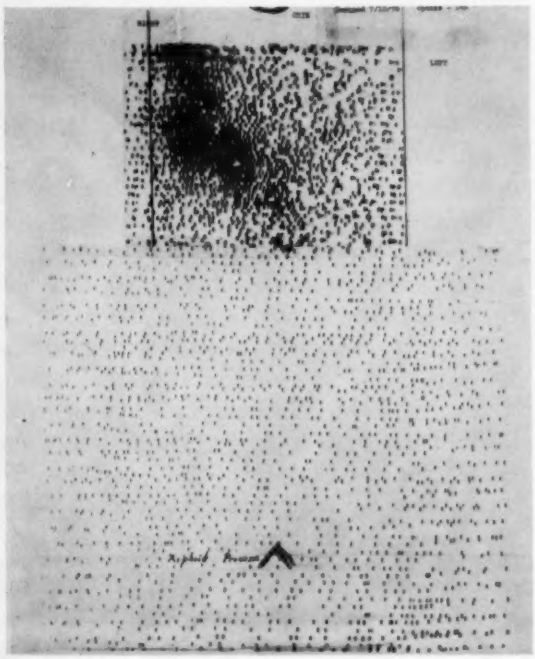

FIG. 12. Case IV. Scintigram in July, 1956 shows deposition of radioiodine.

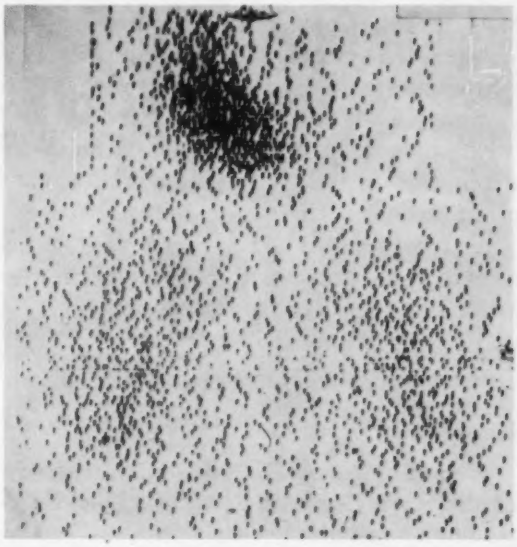

FIG. 13. Case IV. Scintigram in December, 1958 clearly shows evidence of localization in the right lobe of the thyroid, in the cervical lymph nodes and in the pulmonary parenchyma.

SUMMARY

The case histories of 4 patients with metastatic thyroid cancer in the lung show-

ing radioiodine concentration are described. The roentgenographic appearance of the chests of 3 patients have returned to normal. Two patients are alive and well without evidence of disease nine years after the initial radioiodine therapy. A third patient is free of the disease two years after treatment. The relation of radioiodine therapy to the possible prolongation of these patients' lives is discussed.

Simon Kramer, M.D.
Jefferson Medical College Hospital
Department of Radiology
Philadelphia 7, Pennsylvania

We wish to thank Professor D. W. Smithers of the Royal Marsden Hospital, London, for permission to publish a follow-up study of the first patient in this report. Dr. Eberhard treated the second patient and was responsible for the initial treatment of the fourth patient. We wish to acknowledge the interest and help of Dr. Karl Paschkis in the management of the patients treated at Jefferson Hospital.

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BIOLOGIC EFFECT OF GRID COBALT 60 RADIATION*

By JOHN W. LANE, M.D.,† WALTER MAUDERLI, D.Sc.,‡ *and* DAVID M. GOULD, M.D.§
LITTLE ROCK, ARKANSAS

THE modification of conventional deep roentgen-ray therapy beams by means of a lead grid has been thoroughly studied for a number of years. The similar modification of supervoltage cobalt 60 beams, however, has not been so thoroughly investigated. Only a single clinical study and no biologic data were found in a recent review of the literature. Beginning in 1957 a program was initiated at this institution to investigate the clinical effects of grid telecobalt therapy as a palliative procedure upon selected cases of far advanced carcinoma.[1] The early results were so encouraging that the program was expanded and parallel studies of physical dosimetry and biologic effects were initiated.[3,4]

Although it was felt that larger animals would be more suitable for study of the grid effect, it was decided that a pilot study using mice might first be accomplished. This paper is a report of the results of this initial study; a more elaborate program with larger animals is planned.

EXPERIMENTAL METHODS AND MATERIALS

A widely accepted and well established end point for determining the effects of radiation upon animals is the concept of the LD 50/30 (the dose required to kill 50 per cent of the exposed animals within a thirty day period). Male, white, Swiss mice of the Webster strain* were divided into two approximately equal experimental groups. The age range of the mice at time of exposure was fourteen to twenty weeks. Both groups were anesthetized with intraperitoneal nembutal and divided into subgroups. One group was exposed to graduated doses of homogeneous cobalt 60 radiation. The other group was exposed under identical conditions except that the cobalt 60 radiation was modified by a lead grid (Table I and Fig. 1). Anesthesia was deemed necessary to insure immobility of the animal and constant position of the grid beam. The physical characteristics of the lead grid are summarized in Table II.[4] The animals were closely observed and if motion was noted during grid irradiation those mice were removed from the study. Animals dying during exposure or within the first twelve hours after exposure were

TABLE I
EXPOSURE DATA

Homogeneous Exposure	Total No. of Mice	30 Day Mortality	Corrected 30 Day Mortality	Percentage 30 Day Mortality	Mean Survival Time (Da.)
Controls	49	1	0	0	400
500 r	51	9	8±2.6	16±5.1	57
600 r	50	10	9±2.7	18±5.4	56
700 r	50	20	19±3.4	38±6.9	38
800 r	54	31	29±3.7	54±6.8	22
900 r	49	39	37±6.1	76±6.1	14
Grid Exposure					
Controls	51	1	0	0	400
1,500 r	12	1	1±1	8.3±8.3	>76
1,600 r	14	4	4±1.8	35±12.7	58
1,700 r	14	4	4±1.8	35±12.7	47
1,800 r	51	22	21±3.5	41±6.9	45
2,100 r	50	34	33±3.4	66±6.7	16
2,400 r	47	46	45±1	98±2.2	6

* Obtained from the Maple Grove Rabbitry in Springfield, Missouri.

* From the University of Arkansas Medical Center, Little Rock, Arkansas. This work was carried out with the assistance of grants from the Atomic Energy Commission (Grant #AT-(40-1)-1771) and the American Cancer Society (Institutional Grant #IN-1).
† Assistant Professor of Radiology. Work completed under an American Cancer Society Fellowship (CF 802).
‡ Assistant Professor of Radiation Physics.
§ Professor and Head of Radiology.

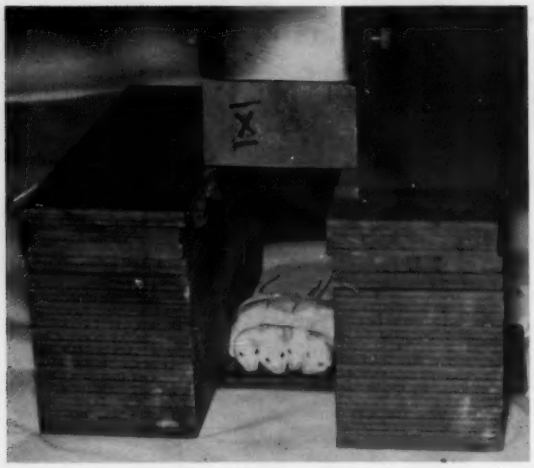

Fig. 1. Experimental setup for grid irradiation.

considered anesthesia deaths and were also eliminated from the study. Following exposure, the animals were caged in groups of 5 and observed daily for time of death. The animals received mouse chow and water *ad libitum*.

Approximately 700 curies of cobalt 60 housed in a Barnes-Keleket Telecobalt Therapy Unit was the radiation source. The following exposure factors were used: source-animal distance was 50 cm.; dose rate of the homogeneous beam was 52.5 r/min.; the grid dose rate was 31.2 r/min. Dose measurements for the homogeneous beams were made with Victoreen chambers at the center of the open field. In grid fields, dose measurements were made by film dosimetry in the axis of the center grid hole.[4] All doses presented in this study, unless otherwise indicated, were measured in this way. The exposure conditions are schematically shown in Figure 2.

Table II

Physical characteristics of lead grid

	Grid-1	
Hole diameter	6.35 mm.	
d, Source side d′, Patient side	8.9 mm. 10.5 mm.	
Area ratio: L/h Source side Patient side	 1.5 2.5	
Field size for 50 per cent intensity at 50 cm. from source	15 mm.	
D, 50 cm. from source	15 mm.	
Area ratio: L′/h′	0.3	
Dose in hole center in per cent of dose in open field	59.5	
Depth in cm.	A	B
0.4	47.4	25.1
3.5	64.2	36.0
6.9	71.7	45.4
10.7	79.9	53.1
15.2	91.7	66.7
19.0	94.2	74.8

RESULTS

The data for the determination of the LD 50/30 are presented in Table 1. The LD 50/30 for the homogeneous irradiation is 775 ± 50 r. This value is surprisingly large but might be explained by the effects of anesthesia. In the first place, the anesthesia produces a relative anoxia and

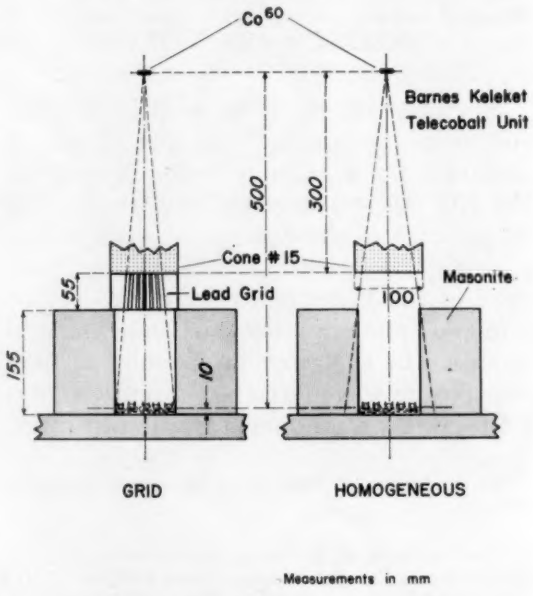

Fig. 2. Schematic representation of irradiation geometry.

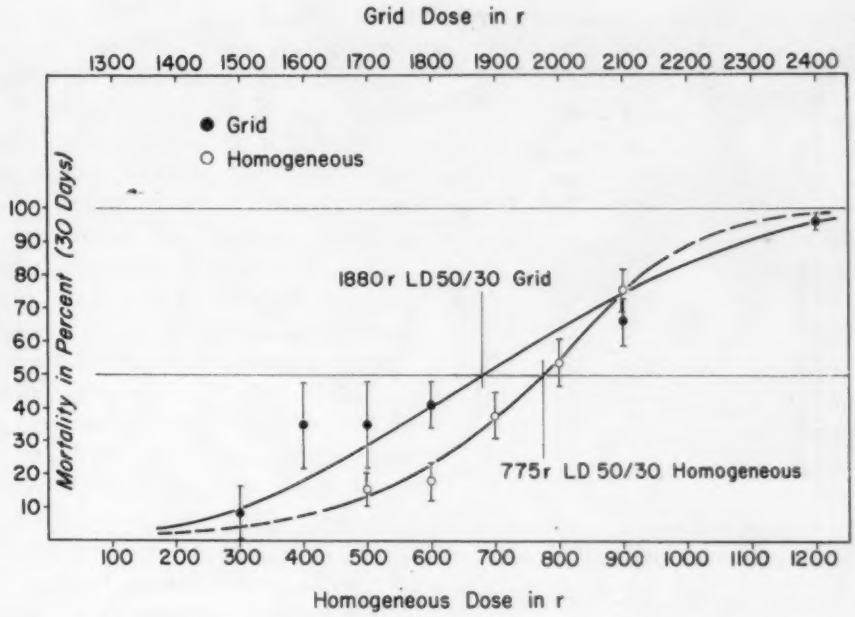

FIG. 3. Mortality curves for LD 50/30 determination—equal linear axes.

lowered metabolic rate which has been shown to result in a decrease of an animal's susceptibility to the effects of radiation. Another effect would be the loss of the less hardy animals by anesthesia and their subsequent removal from the study. The loss of these animals would produce a selected population of healthier mice more resistant to radiation effects. The LD 50/30 for grid irradiation is 1,880 ± 100 r. Thus, the dose ratio of grid radiation to homogeneous radiation to produce a similar effect is 2.4:1. For lower doses this ratio increases to 2.9, whereas at higher doses it decreases to 2.2. The mortality curves are presented in Figures 3 and 4. (Figure 5 shows a probit analysis plot of the LD 50/30 data.) In Figure 3, both groups are plotted on the same linear horizontal axis scales; whereas in Figure 4 the grid scale has been modified by division of the original linear scale by 2.4 (or the grid to homogeneous ratio of LD 50/30 doses). By this manipulation the curves are seen to be similar and nearly superimposed. This congruence implies similar general reactions of the animals to both types of radiation; the grid radiation is simply less effective by a variable dose-dependent factor. This factor is shown plotted versus probits in Figure 6.

Mean survival times were computed and grid and homogeneous radiation doses required to produce the same mean survival time were examined. The mean survival time is plotted against grid and homogeneous dose in Figure 7. (Figure 8 shows the same information in a probit analysis plot assuming the mean normal survival of the mice to be four hundred days.) The ratios are again seen to be dependent upon dose and at the LD 50/30 dose range (probit 3.5) the ratio is 2.5 compared to 2.4 for that derived by LD 50/30 determination.

Thus, the data indicate that, to produce the same lethal effect, groups of mice exposed to whole body grid radiation require 2.2–2.9 times more exposure (depending upon dose delivered) than is required by groups exposed to homogeneous beams.

DISCUSSION

A review of the recent literature revealed only one study of this type. In 1958 Sakka and Kamata[5] exposed rats to 170 kv. (constant potential) roentgen rays modified by a 3 mm. thick lead grid. The grid holes were

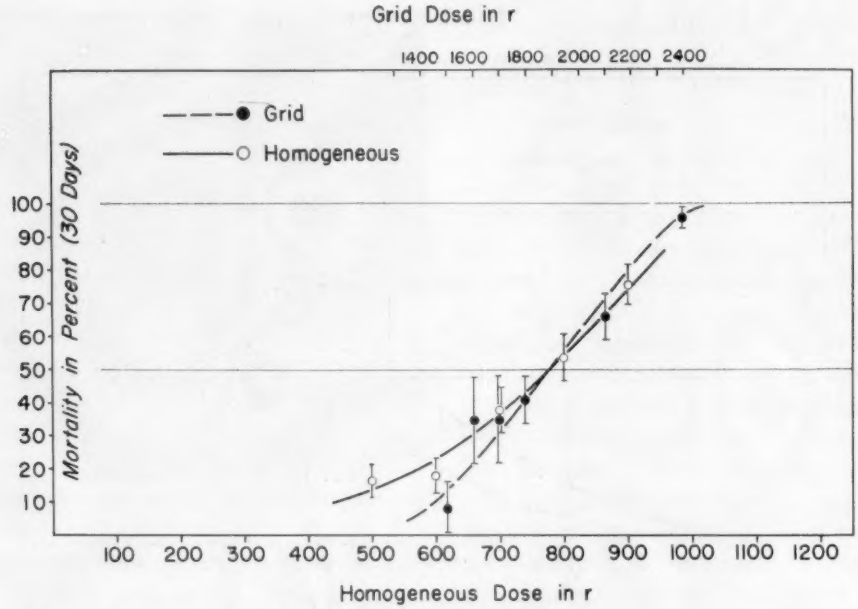

FIG. 4. Mortality curves for LD 50/30 determination, axis representing grid dose modified by division by 2.4.

8 mm. in diameter and were separated by 1 cm. resulting in an exposed to shielded area ratio of 1:1. They reported that a grid to homogeneous dose ratio of approximately 3:1 was necessary to produce the same lethality based upon LD 50/30 determination. No reported studies utilizing supervoltage radiation were found.

Calculations of volume (or integral) doses of both the homogeneous and grid

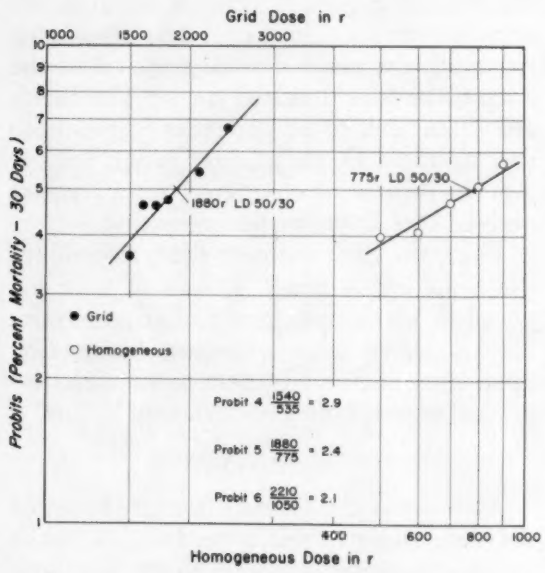

FIG. 5. Probit analysis plot of LD 50/30 mortality curves.

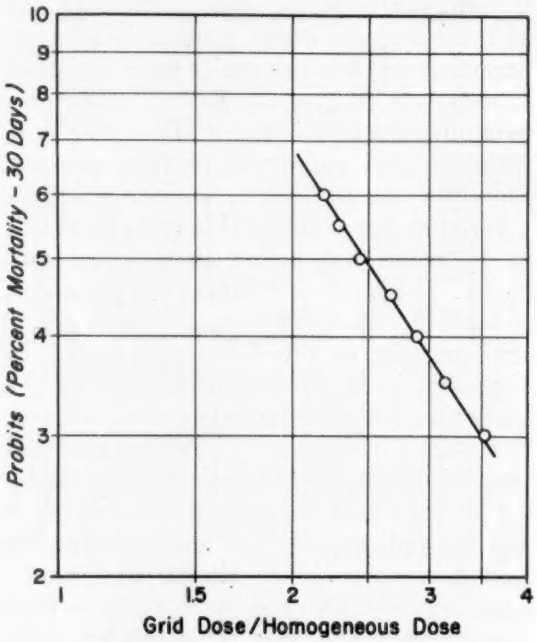

FIG. 6. Grid to homogeneous LD 50/30 dose ratio plotted versus probits of dose.

exposures were done.[4] One might intuitively expect that the dose requirements for a given effect would be directly and solely dependent upon the volume dose. If this be true, then grid and homogeneous exposures should produce the same effect for equal volume doses. Similarly, one would expect that the ratio of grid to homogeneous exposure (for the same biologic effect) would be a constant one and independent of dose level. Neither of these assumptions was found to fit our experimental results.

For the same measured dose, the volume dose ratio of grid to homogeneous exposure was found to be 0.53 (Fig. 9). However, it was previously shown that 2.4 times the homogeneous dose must be given a grid field for a given biologic effect. Thus, the volume dose necessary for the same biologic effect with the grid beam is 2.4×0.53, or 1.3 times greater than with homogeneous radiation. It follows that the grid beam is only 1/1.3, or 0.77, times as effective biologically as the homogeneous beam and the volume dose of grid radiation must then be increased by approximately 30 per cent to yield an exposure of equal biologic effect as the same volume dose of homogeneous radiation. This implies a relative tissue sparing effect inherent in grid exposures over and above volume dose differences. In

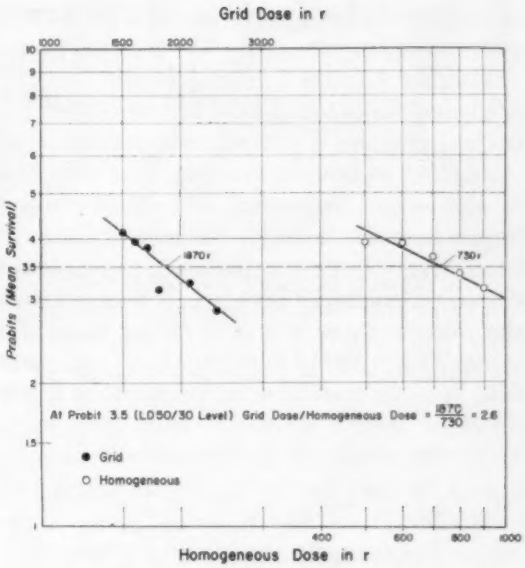

Fig. 8. Probit analysis curves of mean survival time data.

1954 Kereiakes *et al.*[2] exposed rats to homogeneous and grid modified 200 kv. peak roentgen rays and reported a similar sparing effect. It is felt that perhaps the network of relatively nonirradiated tissue might be responsible for this effect much in the same way that one spares skin in conventional roentgen-ray therapy by use of the lead grid.

From the foregoing, it appears that with grid radiation it is possible to deliver large doses to cores of tissues with less over-all

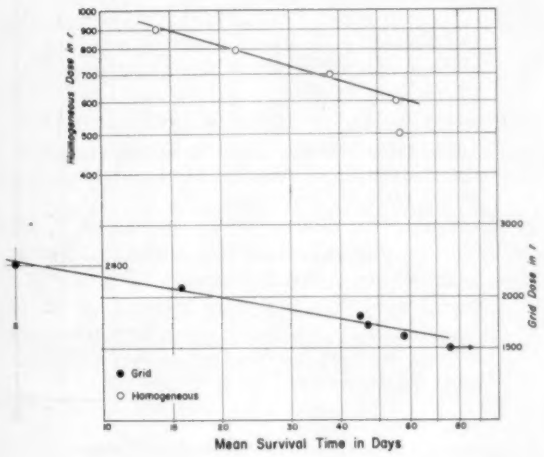

Fig. 7. Mean survival curves for grid and homogeneous radiation doses.

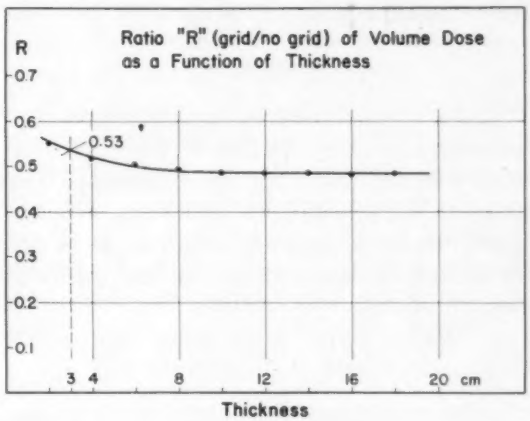

Fig. 9. Volume dose ratio (grid/homogeneous) versus thickness of target.

systemic effect than is possible with homogeneous radiation.

Further studies utilizing larger animals are being initiated. These are necessary for several reasons. First, the extrapolation of mice data to man is hazardous at best but is somewhat improved by studies upon larger animals. Second, the size of the grid is relatively large compared to the over-all size of the mouse. Therefore, it was felt that the placement of the grid might place the spleen completely within the radiation field in some instances or, perhaps, at other times it might shield it from exposure. Thus, the resultant data might be heavily biased by the effect of spleen shielding and not reflect true whole body exposure results. However, the grid used in this study was the smallest practicable and would necessitate using larger animals as the only means of overcoming this possible objection.

In view of the results reported above it is interesting to compare the ratio of grid to homogeneous exposures in this study to that ratio applied during clinical exposures. Doses utilized in homogeneous irradiation were multiplied by 3 for grid exposure on advanced cancer patients and the clinical results seem to justify this ratio. This ratio of 3 correlates very nicely with the ratio of 2.9 obtained from this study in the lower dose ranges (400–600 r) which is the usual daily dose range used in conventional cobalt teletherapy.

SUMMARY

1. In a recent clinical study a group of advanced cancer patients were treated with focused telecobalt grid therapy. The relative biologic effect of grid therapy compared to homogeneous irradiation is unknown and this report is an initial study of this problem.

2. White Swiss mice were exposed in comparable groups to homogeneous and grid cobalt 60 radiation.

3. The ratio of the grid dose to the homogeneous dose required to produce a median 30 day lethality was found to be 2.4. This factor, however, was dependent upon total dose and varied from 2.9 at lower doses (400–600 r) to 2.2 at higher doses (900–1,000 r).

4. Analysis of mean survival times of the 2 groups of mice revealed a ratio of 2.5 at the LD 50/30 dose level.

5. The volume dose for grid exposure was found to be 1.9 times less than that delivered by equal homogeneous doses. Thus, a sparing effect of grid irradiation was suggested by the discrepancy of the ratios of 1.9 and 2.4.

6. The ratio of 2.9 (lower dose range ratio) is close to that found to be clinically effective in the clinical cancer study.

7. Further studies upon larger animals would be a logical and almost mandatory extension of this work.

David M. Gould, M.D.
Department of Radiology
University of Colorado Medical Center
4200 East Ninth Avenue
Denver 20, Colorado

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A CRITICAL APPRAISAL OF THE DIAGNOSTIC AND PROGNOSTIC VALUE OF RADIOIRON STUDY IN HEMATOLOGIC DISORDERS*

By CHING TSENG TENG, M.D.,† VINCENT P. COLLINS, M.D., *and* WALTON D. WEST, M.S.
HOUSTON, TEXAS

THE average life span of normal human red blood cells has been accepted as one hundred and twenty days.[1,3] This means that in a steady state 100/120, or 0.83 per cent, of the circulating red blood cells are destroyed and replaced daily. This physiologic phenomenon occurring continually throughout life involves two major processes: (1) the destruction of senile, injured and defective red blood cells with the degradation of the liberated hemoglobin, and (2) the production of new red blood cells and the synthesis of new hemoglobin.

Under normal circumstances, the rate of erythropoiesis matches the rate of erythrolysis, thus maintaining a remarkable constancy of red blood cell mass and hemoglobin concentration. For an adult man, this means the destruction and replacement of 21 billion red blood cells, the degradation and synthesis of 6.2 grams of hemoglobin and a turnover of 21 milligrams of iron per day (Table I).

Under pathologic conditions, imbalance of these rates leads to disease: excessive production results in polycythemia; increased destruction or diminished production (or loss by hemorrhage) leads to anemia.

Direct measurement of these rates has recently become possible with the use of isotopes of nitrogen,[30,39] carbon,[2] iron,[10,11,15,18] chromium,[13,33,41] phosphorus,[4,5] and others.[3] These studies have increased our understanding of iron and hemoglobin metabolism in health and disease and have provided information of diagnostic and prognostic value not available from conventional hematologic studies.

TABLE I

NORMAL ERYTHROPOIESIS IN A 70 KG. MAN

Observed data

(a) Rate of red blood cell replacement: 0.83×10^{-2}/day
(b) Blood volume: 5×10^3 ml.
(c) Red blood cell count: 5×10^6/mm.^{3} $= 5 \times 10^9$/ml.
(d) Hemoglobin concentration: 15 gm.% $= 15 \times 10^{-2}$/ml.
(e) Hemoglobin iron: 3.34 mg. iron/gm. Hb

Calculated data

(f) Number of red blood cells destroyed and replaced $= (a) \times (b) \times (c) = 21 \times 10^{10}$ red blood cells/day
(g) Amount of hemoglobin degraded and synthesized $= (a) \times (b) \times (d) = 6.2$ gm./day
(h) Amount of iron required $= (g) \times (e) = 21$ mg./day

THE HEMOGLOBIN CYCLE OF IRON METABOLISM

The metabolism of hemoglobin is intimately related to the metabolism of iron. According to Granick,[12] the total body iron in an adult man ranges from 3 to 5 gm. Of this the hemoglobin iron (2–3 gm.) represents 60–70 per cent and the serum iron (3–4 mg.) less than 0.1 per cent.

The so-called hemoglobin cycle[23,24,34,40] consists of the following steps:

(1) The transportation of plasma iron to the bone marrow. Although the plasma iron pool[11] is in equilibrium with all compartments of body iron, up to 90 per cent of iron transported is destined for the bone marrow.[10,11]

(2) The synthesis of hemoglobin with

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† Present address: Department of Radiology, Texas Children's Hospital and St. Luke's Episcopal Hospital, Houston, Texas.

iron available in the bone marrow during erythropoiesis.

(3) The degradation of hemoglobin and liberation of iron in the reticuloendothelial system, mainly the spleen, where senile and defective red cells are destroyed.

(4) The transportation of iron from the sites of red blood cell destruction (and from organs of iron storage and absorption) to the plasma pool. Recycling of hemoglobin iron constitutes 70 per cent or more of the iron utilized in erythropoiesis.[6,7,11,14,38]

The plasma iron of an adult man totals about 3–4 mg. The daily requirement of iron for erythropoiesis is about 21–25 mg. (Table 1). Iron must continually leave the plasma pool to supply the need of the bone marrow; an equal amount of iron must continually enter the plasma pool from the spleen, the liver, and the gastrointestinal tract to replenish the loss and maintain the concentration of plasma iron.

When the plasma iron pool is labeled with radioiron, the rate of iron leaving the plasma pool and the rate of iron utilized in erythropoiesis may be determined.

The disappearance of radioiron from the plasma pool is a logarithmic function of time. The disappearance rate (k) and disappearance half time (T) are related in the familiar equation: $kT=0.693$. With a few exceptions, each is a reflection of the demand for iron by the bone marrow and an indirect index of the rate of erythropoiesis.

A more direct and more accurate index of erythropoietic activity is the rate of utilization of iron in hemoglobin synthesis. This is commonly reported as per cent uptake or incorporation of the administered radioiron by newly formed red cells.

METHOD AND CALCULATIONS

Labeling of Plasma Iron. Several methods for the labeling of plasma iron with Fe^{59} have been described.[18,29,36,40,44] We have used both the *in vitro* and the *in vivo* procedures with equally satisfactory results.

In the *in vitro* procedure, 20–30 ml. of the patient's own blood is drawn into a sterile syringe containing a measured amount of a buffered Fe^{59}-citrate solution with about 5 μc of radioactivity.[29] After thirty minutes of incubation at room temperature, practically all of the added Fe^{59} will have combined with an excess of apoferrin, a B_1-globulin, in the plasma: Fe^{59}+apoferrin $=Fe^{59}$-transferrin.[23,24]

After a control blood sample has been obtained, the incubated mixture is injected intravenously. The syringe is rinsed with venous blood several times to insure complete delivery.

An *in vivo* method of labeling the plasma iron was introduced by our laboratory.[29] This procedure is simpler: a measured amount of sterile buffered Fe^{59}-citrate solution is injected intravenously after a control blood sample has been obtained; again, complete delivery of the tracer is insured by rinsing the syringe. Tagging of the circulating plasma apoferrin *in vivo* takes place very rapidly.

The Plasma Iron Disappearance Curve. Following the injection of radioiron by either procedure, 4 to 6 blood samples are obtained with heparinized syringes at intervals of five to fifteen minutes. Equal aliquots (1.0–2.0 ml.) of plasma from these and the control blood samples are assayed for radioactivity in a well type scintillation counter. The radioactivity (cpm) of the samples is corrected for that of a control blood sample. The corrected values are plotted on a log scale against time on a linear scale. The best straight line is drawn through the observed points. The slope of this line is the rate (k) of plasma iron disappearance. The zero time plasma radioactivity is obtained by extrapolation. The disappearance half time (T) may then be read off the curve (Fig. 1). The normal values for T range from sixty to one hundred and twenty minutes.

Aliquots of whole blood taken from the control and one or more postinjection blood samples are similarly counted and the corrected data plotted. The slope of the whole blood curve should be identical to that of the plasma curve of radioiron disappearance. The radioactivity of whole blood at zero time is similarly obtained by extrapolation.

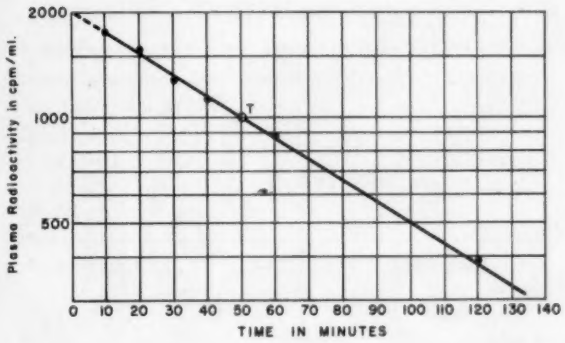

Fig. 1. Plasma radioiron disappearance curve. Dotted line extends disappearance curve (solid line) to zero time ordinate; the intersect gives extrapolated zero time plasma radioactivity—2,000 cpm/ml. The disappearance half time (*T*) shown by open circle is found on the curve where the plasma radioactivity reaches 1,000 cpm/ml., or 50 per cent of the zero time value, at fifty minutes after injection.

The Per Cent Red Blood Cell Uptake of Radioiron. Follow-up blood samples are obtained at frequent intervals up to two weeks or longer. Aliquots of these samples (whole blood) are counted and corrected for room background or control blood sample radioactivity. The per cent red blood cell uptake is calculated as follows:

$$\text{Per cent uptake} = \frac{\text{Corrected cpm/ml. blood on follow-up day} \times 100}{\text{Corrected cpm/ml. blood at zero time*}}$$

The normal values for red blood cell uptake range from 80 to 100 per cent in seven to ten days.

A number of other indices may be calculated from the radioiron data and plasma iron concentration.[18] These will not be discussed here.

CLINICAL STUDIES

Radioiron studies have been carried out on a large number of patients in our laboratory. The studies on cancer patients receiving whole body and limited field roentgen therapy have been reported previously.[28] Studies of sickle cell anemia and various types of hemolytic anemia are in progress and will be reported in another paper. The observations in iron deficiency anemia, aplastic anemia, pernicious anemia, and secondary polycythemia are presented below.

Table II

Observations in 10 Children with Iron Deficiency Anemia

	Range	Mean
Hematologic Findings		
Hemoglobin, gm. %	1.9–9.5	6.5
Hematocrit, %	9–35	26
Plasma iron, μg. %	18–65	39.5
Radioiron Data		
Plasma iron disappearance halftime (*T*) in minutes	12–43	22
Red blood cell uptake of radioiron		
% in 3 days	32–70	58
% in 7 days	88–100	96

(A) *Iron Deficiency Anemia.*[7,8,10,12,22,25,35,44] A group of 10 children, 5 male and 5 female, with iron deficiency anemia have been studied in collaboration with Dr. Charles W. Daeschner, Jr. The pertinent data are summarized in Table II.

Besides the moderate degree of hypoferremia and anemia, other common features in this group are (1) rapid rate of plasma iron disappearance as indicated by the shortened disappearance half time (Fig. 2), and (2) rapid rate and maximum red blood cell uptake of radioiron (Fig. 3). These findings indirectly and directly portrayed the increased rate of erythropoiesis. Bone marrow studies were done in 6 patients; 4 revealed marked erythroid hyperplasia.

(B) *Aplastic and Myelophthisic Anemias.*[7,8,10,18,37,38,41,43,44] The observations in 6 patients with aplastic or refractory anemia of varying etiology are summarized in Table III. In sharp contrast to iron defi-

* Correction for physical decay to day of follow-up by multiplying with the decay factor:

$$\frac{\text{cpm/ml. reference standard on follow-up day}}{\text{cpm/ml. reference standard on day zero}}$$

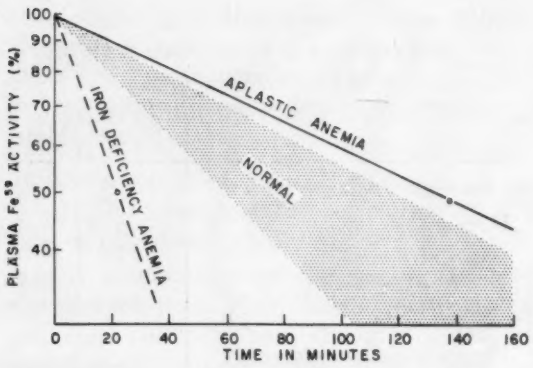

Fig. 2. The markedly reduced incorporation of radioiron in aplastic anemia is direct evidence of diminished erythropoiesis due to bone marrow aplasia or hypoplasia. Increased incorporation of radioiron indicating enhanced erythropoiesis is also observed in many other conditions besides iron deficiency anemia.

Table III

Observations in 6 patients with aplastic anemia

Etiology	Hb. (gm. %)	Serum Iron (μg. %)	Plasma Fe^{59} Half time (hr.)	Red Blood Cell Uptake (% in days)
Idiopathic (?)	5.8	154	2.2	22 in 10
Toxic (Benzene)	5.4	265	3.7	6 in 15
Acute Leukemia	4.6	177	3.8	20 in 8
Cystinuria	6.4	62	4.2	22 in 21
Gaucher's Disease*	7.0	168	0.4	28 in 38
Post-radiation	11	170	1.3	46 in 16

* Bone marrow: erythropoietic hyperplasia.

ciency anemia, (1) the plasma iron disappearance rate was decreased (*T* increased) as shown in Figure 2, (2) the red blood cell uptake of radioiron was sluggish and diminished (Fig. 3), and (3) the plasma iron concentration was increased. These findings are expected as erythropoiesis is markedly decreased because of myelophthisis, hypoplasia, or aplasia.

Much reliance has been placed on the histologic picture of the bone marrow for the diagnosis of refractory anemias. Occasionally, however, the findings may be equivocal as the biopsy specimen may not be representative of the entire organ. The functional indices revealed by the radioiron studies are more diagnostic of the total erythropoietic function. This was true in a patient with Gaucher's disease in whom one bone marrow biopsy showed erythroid hyperplasia when the hemogram was consistent with myelophthisic anemia and the radioiron data indicated markedly reduced erythropoiesis.

(C) *Pernicious Anemia.*[7–10,12,15,30,43] Of the patients with pernicious anemia we have studied, 1 case was particularly instructive and merits presentation in some detail.

Case 1. S.S., Hospital No. 3234, a seventy year old white woman, was found to have pernicious anemia while being treated for obstructive jaundice in the hospital. Radioiron studies were carried out (a) before specific treatment was instituted, (b) during vitamin B_{12} therapy while the patient was making a satisfactory recovery, and (c) after complete remission was obtained. The pertinent data are summarized in Table IV.

Comment. (1) In contrast to the preceding groups of patients in whom the rates of plasma iron disappearance and red blood cell uptake showed parallel changes, in the pernicious anemia patient prior to specific therapy these rate changes were dissociated. The increased rate of plasma iron disappearance suggesting increased bone marrow activity was coupled with a decreased

Table IV

Observations in 1 patient with pernicious anemia

	Before	During B_{12} Therapy	Maintenance B_{12} plus Iron Therapy
Hemoglobin, gm. %	4.9	10.2	17.2
Reticulocyte, %	0.7	16.3	1.1
Serum Iron, μg. %	163–176	33–38	172–182
Radioiron, *T* (min.)	32	20	102
Radioiron Uptake, % days	21/14	77/4	67/5

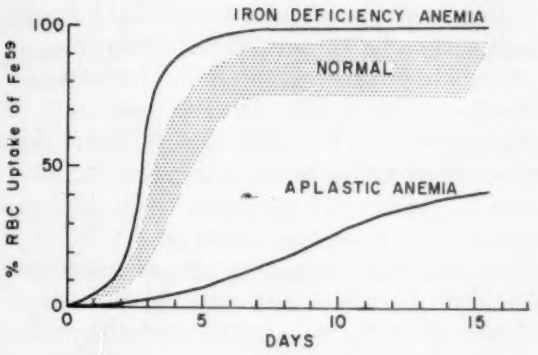

Fig. 3. The rate of disappearance of plasma iron is increased in iron deficiency anemia and decreased in aplastic anemia in keeping with the demand for iron by the bone marrow for increased and decreased erythropoiesis in these conditions respectively.

rate of red blood cell uptake indicating reduced hemoglobin synthesis. These seemingly paradoxical findings are in keeping with the basic pathophysiology of pernicious anemia, namely, megaloblastosis, maturation arrest, and inability to incorporate iron.[9,16,24]

(2) The remarkable speed of hematologic recovery following vitamin B_{12} therapy was accompanied by the development of a marked degree of hypoferremia. As the maturation process was returning to normal, the utilization of iron was greatly speeded up. This lowered the plasma iron concentration[16,24] which in turn further stimulated the rate of plasma iron disappearance.

(3) When the patient had achieved complete remission after the addition of iron therapy,[32] normalcy of erythropoietic function was reflected by the results of the third study.

From the physiologic point of view, these studies have provided information accurately portraying the pathologic disturbances in pernicious anemia and the physiologic adjustment in response to vitamin B_{12} and iron therapy.

(D) *Secondary Polycythemia.*[19,21,25–27,31,37,42] Two patients with secondary polycythemia have been studied with radioiron. They showed very different results although the degree of erythremia was about the same.

Case 2. O.S., Hospital No. CE 9229, a fifteen year old Mexican boy, was admitted to the hospital with the diagnosis of congenital heart disease involving the tricuspid valve and a probable right to left shunt. He had had intense cyanosis since birth and repeated episodes of congestive heart failure in recent years. Hematologic studies revealed a marked degree of polycythemia. Radioiron studies showed a greatly increased rate of plasma iron disappearance, a rapid red blood cell uptake of iron, and a low plasma iron concentration. These findings are shown in Table v and Figures 4 and 5.

Case 3. M.B., Hospital No. CH 1166, a twenty-eight year old white man, was admitted to the Polio Service as a case of postpolio hypoventilation syndrome. One year previously he had had acute anterior poliomyelitis with muscular paralysis involving the diaphragm and below. He recovered sufficiently to become ambulatory after three months of hospitalization and went to Mexico City to live with his sister. As he increased his physical activities there, he soon developed marked cardiac and respiratory symptoms with the findings of severe secondary polycythemia. He returned to Houston and was hospitalized here. After three weeks of treatment with oxygen therapy and a mechanical respiratory apparatus, his symptoms gradually subsided, but the hematologic evidence of polycythemia persisted. These data are shown in Table v. The radioiron study performed at this time seemed at variance with the peripheral blood picture: the plasma iron disappearance half time was normal; red blood

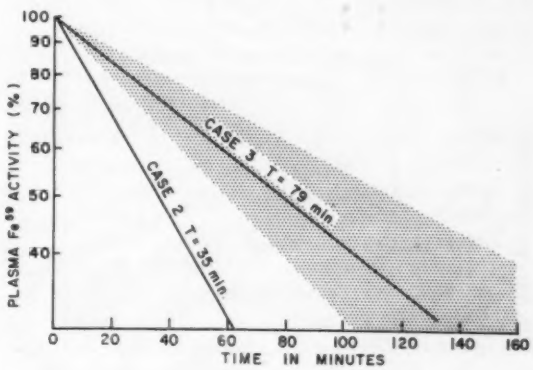

Fig. 4. A comparison of red blood cell uptake of radioiron in 2 cases of secondary polycythemia and normal subjects. See text for discussion of the markedly diminished incorporation of radioiron in Case 3.

TABLE V

OBSERVATIONS IN 2 PATIENTS WITH SECONDARY POLYCYTHEMIA

	Case 2	Case 3	
Clinical Diagnosis	Cyanotic congenital heart disease	Postpolio hypoventilation syndrome	
Period of Observation	March 1955	February 1956	March 1956
Vital Capacity, ml.		1,100	2,600
Hemoglobin, gm. %	17–19	18–20	14.4
Hematocrit, %	60–65	68–75	46
Plasma Iron, μg. %	60–66	350–410	
Radioiron Study, *T* (min.)	35	79	
Red Blood Cell Uptake, % in Days	100 in 7	10 in 5 28 in 19 43 in 30	

cell uptake of iron was markedly decreased. These data are shown in Figures 4 and 5.

The patient continued to improve. His vital capacity rose from 1,100 to 2,600 ml. and gradually his polycythemia subsided completely in the course of six weeks of observation following the initial studies. These data are also shown in Table v.

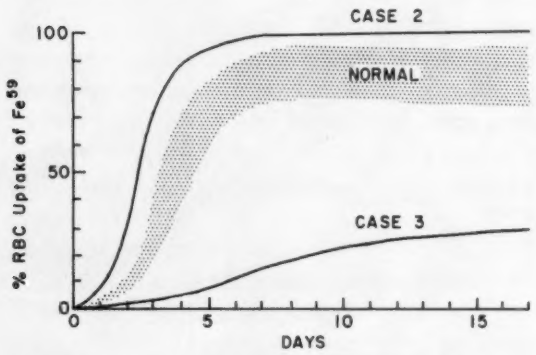

FIG. 5. A comparison of plasma radioiron disappearance in 2 cases of secondary polycythemia and normal subjects. See text for discussion of the normal rate of disappearance in Case 3.

Comment. In these 2 cases of secondary polycythemia, the degree of erythremia as revealed by the hematocrit and hemoglobin levels is quite similar. The radioiron data in the boy with cyanotic congenital heart disease are as would be expected, but the findings in the postpolio patient seem quite incompatible with the degree of erythremia observed. However, the postpolio patient had been at rest, at the sea level altitude of Houston, and in a respirator for three weeks. The stimulus of anoxia and the demand for increased erythropoiesis had been withdrawn.[26,31] The normal plasma iron disappearance rate and the sluggish red cell uptake of iron indicated relative inactivity of the bone marrow, even though it was six weeks before the hematologic abnormalities finally returned to normal levels. From a prognostic point of view, the radioiron study anticipated the eventual recovery several weeks before it was evident in the peripheral blood picture. The remarkable sensitivity of the radioiron study in detecting functional changes of erythropoiesis is again demonstrated.

DISCUSSION

As all students of physiology and medicine realize, functional studies—pulmonary, cardiac, hepatic, renal, thyroid, etc.—generally provide information with regard to the over-all activity of the organ or system under investigation and the direction and magnitude of change or deviation from the normal range. They rarely furnish information of a specific nature in respect to the etiology or morphology of the disease which causes the change in functional activity. This is understandable as different etiologic factors may cause identical structural changes and varying pathology may lead to similar functional disorder. It follows that functional tests must be interpreted with caution and in corroboration with other available data.

The appraisal of radioiron study or erythropoietic function should follow this general concept. Evaluated on such a basis, the functional indices derived from a radioiron tracer study are of diagnostic and prog-

nostic significance in a number of hematologic disorders, as has been demonstrated in this paper.

SUMMARY AND CONCLUSIONS

1. Certain basic information on erythropoiesis and hemoglobin and iron metabolism pertinent to the radioiron tracer study has been briefly presented.

2. The procedure of the study and the method of determination of the functional indices of erythropoiesis with radioiron (Fe^{59}) as the tracer have been described.

3. These indices measure the rates of iron and hemoglobin metabolism, introduce the dimension of time and portray a dynamic picture of physiologic and pathophysiologic changes of erythropoietic function.

4. Observations in 10 patients with iron deficiency anemia, 5 patients with aplastic or myelophthisic anemia, 1 patient with pernicious anemia studied before specific treatment, during vitamin B_{12} therapy and after complete remission, and 2 patients with secondary polycythemia have been presented.

5. The sensitivity of the radioiron study as a measure of changes of erythropoietic activity has been demonstrated.

6. The pathophysiologic significance of the observations and their diagnostic and prognostic value have been discussed.

Ching Tseng Teng, M.D.
St. Luke's Episcopal Hospital
Houston, Texas

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THE EFFECT OF L-TRIIODOTHYRONINE ON RADIATION SENSITIVITY*

By MELVIN L. GRIEM, M.D.,† *and* JOSEPH A. STEIN, M.D.‡
CHICAGO, ILLINOIS

VARIOUS modifying agents have been used to effect a change in the reaction of tissues to radiation. The effect of oxygen in altering the radiosensitivity has been well documented by Gray[5] and Churchill-Davidson and co-workers.[3] It can be summarized, in general, by saying that when tissue oxygenation is increased at the time of irradiation there is an increase in radiation effect.

While data on the protective action of myxedema are not extensive, the hyperthyroid state has been shown to hasten mortality in mice given acute lethal doses of total body irradiation.[8,9] Although the fundamental mechanism of the action of thyroid hormone is not completely understood, the administration of thyroid hormone produces an increase in metabolic rate (especially of carbohydrate metabolism), in rate of blood flow, in oxygen consumption, and in growth potential as demonstrated by enhanced mitotic activity. Oxygen consumption is not affected to the same degree in all tissues; there is little change in the brain, spleen and testes, while the liver, kidney and muscle all demonstrate increased consumption.[4] It was therefore postulated that stimulation of selected localized tissues might also lead to an increase in the radiosensitivity of these tissues, whether they were normal or neoplastic.

L-3,5,3′-triiodothyronine sodium,§ was selected to induce the hyperthyroid state. Since the hormone acts rapidly at the cellular level,[6] this drug lends itself readily to both experimental and clinical use, rapid induction and ease of control and withdrawal of the induced hyperthyroid state being some of its characteristic properties. It has been demonstrated that human mitochondria convert triiodothyronine into triiodoacetic acid[1] and that there is an influence of triiodothyronine on oxidative phosphorylation of tumor mitochondria.[7]

ANIMAL EXPERIMENTS

Three abnormal tissues were studied in the preliminary investigations, two rat tumors and one mouse tumor.

The first was a solid, nonmetastasizing, nonsystemic, myeloid, chloroleukemia rat tumor.[10] This tissue was injected subcutaneously into the flanks of male, Sprague-Dawley rats weighing 150–250 gm. Within two to three weeks the tumor thus produced attained a size of 2–3 cm., and parenteral administration of triiodothyronine was started. Prior to each experiment, the triiodothyronine was prepared by dissolving it in 1/100 normal NaOH, 1.3 cc. per 5 mg. of the drug, and diluted with saline to a volume of 50 ml., and the pH adjusted to 9. The solution was prepared aseptically, chilled immediately and stored at 4° C. Four consecutive doses of 200 μg. each were given subcutaneously every other day, and the oxygen consumption thus increased 60 to 80 per cent above normal values as determined by a Walton kymograph and spirometer. This dose of triiodothyronine (*i.e.*, 200 μg.×4) proved to be in excess of physiological tolerance and resulted in some mortality even before irradiation.

The rats were irradiated three days after

§ This was kindly supplied as Cytomel by J. Clipson of Smith, Kline and French Laboratories.

* From the Department of Radiology and the Argonne Cancer Research Hospital, The University of Chicago, Chicago, Illinois.
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† American Cancer Society Clinical Fellow and Assistant Professor of Radiology, The University of Chicago, Chicago, Illinois.
‡ Ann Langer Cancer Research Foundation Fellow with the University of Chicago. Present address: The Radium Institute of the Hebrew University, Hadassah Medical School, Jerusalem, Israel.

the last injection of the drug, and were not anesthetized during treatment lest the anesthetic cause changes in metabolic and respiratory rates. Consequently, satisfactory immobilization of the exposed, tumor bearing flank of the rat, caged and treated individually in a protective lead box, was not achieved with certainty in every case. Radiation was delivered at various dose levels above and below the established carcinocidal dose (300 to 1,500 r calculated at 1 cm. depth, 0.2 mm. Cu half-value layer, 150 kv., 21 cm. focal skin distance, 4 cm. cone).

The second tumor investigated was melanoma mouse tumor S-91, derived from the DBA/2 strain mouse from the Jackson Memorial Laboratory, Bar Harbor, Maine, and introduced subcutaneously into the hind leg of animals of the same strain. These 25 gm. animals were subjected to daily injections of 30 μg. triiodothyronine for three days, and on the fourth day, when the metabolism was plus 40 per cent, radiation was administered. Excellent immobilization during irradiation was obtained by the use of a specially designed lead box[2] (Fig. 1) and the design was further improved so that 15 animals could be treated at the same time on a rotating board (Fig. 2). Single doses of 1,000 to 4,000 r in air were used. Radiation was delivered as follows: 250 kv., 1.5 mm. Cu half-value layer, 58 cm. focal skin distance.

The last described method of immobilization and treatment was used on the 250 gm. rats tested in the third set of experiments (Fig. 1). Using a Walker 256 carcinoma-sarcoma, tumor bearing rats were prepared by introducing the tumor into the hind leg rather than into the flank as in the first experiment. When single doses of 1,000 to 4,000 r in air were used, the higher doses produced complete necrosis of the hind leg in both experimental and control animals. Fractionation was then employed as follows: 200 μg. triiodothyronine was given on the first, third, and fifth day; 1,000 r in air on days two, four, and six. The control group of animals received like doses of radiation on alternate days.

Fig. 1. On the left a tumor bearing mouse is shown in its specially designed protective lead box. On the right is a 250 gm. rat with a Walker tumor in its protective lead box.

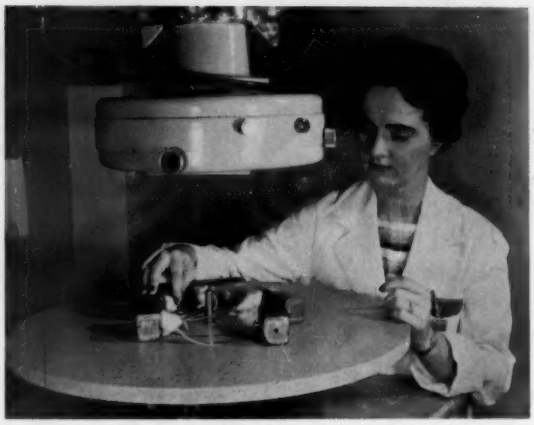

Fig. 2. Typical treatment arrangement using the protective lead boxes on a rotating board.

RESULTS

Of the chloroleukemia animals, only 103 of approximately 400 survived long enough to permit adequate evaluation. Tumor response, judged by simple palpation of the treated site, was evaluated one week after treatment and weekly for eight weeks. Involution of the tumor until it was no longer palpable was found to occur within four weeks if treatment was adequate; otherwise, there was a marked increase in tumor size at this time.[10] Histologic investigation was beyond the scope of this initial project.

In a group of 52 euthyroid rats, the chloroleukemia disappeared when a tumor dose of 1,000 ± 200 rad was given. The same tumor under the same conditions in

51 hyperthyroid rats disappeared when a tumor dose of 500 ± 200 rad was delivered. In neither group did this variation exceed 10 per cent of the total number of animals treated.[10] The few exceptions in each group that were not cured even by the largest doses employed may be attributed to inadequate immobilization during irradiation.

In the melanoma bearing animals, even at the highest doses used, it was not possible to stop tumor growth, either with or without the aid of triiodothyronine. It was noted, however, that the animals treated with triiodothyronine lived somewhat longer.

Using fractionated treatment in the Walker 256 tumor bearing animals, only 1 of a group of 25 survived four months without tumor, when treated with roentgen rays alone. In a like group treated with triiodothyronine and roentgen rays, 5 of 25 animals survived four months without tumor. In an untreated control group of 25 animals, all animals were dead of tumor in twenty-one days.

CLINICAL TESTS

Since the preliminary work on animal tissues suggested that the combination of drug and roentgen therapy provided a satisfactory method of treating certain animal tumors, it was decided to attempt an estimation of its clinical value.

Initially, patients with far advanced cancers who could tolerate an elevated metabolic rate were selected for treatment. Their basal metabolic rates were raised 35 to 40 per cent above normal by oral doses of triiodothyronine beginning with a dose of 200 μg. This dose was increased daily by 50 μg. until the desired basal metabolic rate was obtained and was continued at this level throughout the period of irradiation. Treatment was given in daily fractionated doses. Toxicity due to triiodothyronine and manifested by a sudden decrease in caloric intake, apathy, prostration and lethargy was controlled by decreasing the dosage 100–150 μg., resulting in an immediate regression of the unfavorable symptoms. In several patients, the drug was stopped abruptly without untoward reaction and the basal metabolic rate returned to normal within twenty-four hours.

Two patients with well differentiated squamous cell bronchogenic carcinomas and extensive subcutaneous metastases were chosen for treatment, 1 of whom had symmetric supraclavicular metastases. After induction of the hypermetabolic state, the metastases on one side were treated. At a tumor dose of 1,500 rad, there was marked regression and treatment was suspended at 3,000 rad, a dose not ordinarily considered carcinocidal. The overlying skin also demonstrated an inordinately early and severe radiation response which regressed rapidly after completion of the treatment. This suggests that the skin reaction was also enhanced to some extent. Subsequently, after the hyperthyroid condition had been allowed to return to normal, the metastases on the opposite side were irradiated in a similar fashion, but without administration of the drug. At autopsy three months later, the side subjected to the treatment of a combination of drug and roentgen irradiation showed only fibrosis, while the tumor was still present on the side treated by roentgen rays alone.

Similar observations were made in the second patient, who had extensive lung metastases due to melanoma and was subjected to the combined drug and roentgen treatment. No response was observed when a calculated tumor dose of 2,000 rad was delivered to the lung lesions. Because of the negative results obtained in the experimental animals with melanoma, a higher dose of radiation was not tried on this patient.

Inasmuch as normal brain tissue is not markedly affected by the hyperthyroid state, 2 patients with biopsy proved, well differentiated, adenocarcinoma brain metastases with unknown primary lesions were treated with the combined therapy. These brain lesions responded dramatically with

3,000 to 4,000 rad tumor dose, our usual palliative dose. Although this is not ordinarily carcinocidal for this type of tumor, there has been no recurrence of the brain lesion as observed by clinical evaluation and by isotope localization. In both cases, however, the primary lesion very rapidly became manifest, either during the course of the treatment or very shortly thereafter. This observation, namely, that a tumor untreated by roentgen rays seems to grow much more rapidly when the patient is under the influence of triiodothyronine, has been made in a number of other cases. For this reason, it has been decided that only those patients with inoperable, well localized tumors considered incurable by conventional radiation therapy should now be studied by this method. It is too early to evaluate the results of this current group of patients.

CONCLUSIONS

L-triiodothyronine can be used both experimentally and clinically to produce a qualitative change in the radiosensitivity of certain selected tissues. In the case of melanoma, it was not found possible to potentiate the radiation sensitivity to a degree sufficient to control this tumor. It is hoped that further studies will help to determine the quantitative nature of the sensitivity. The ease with which the metabolic state can be controlled and modified, both experimentally and clinically, by this drug makes it a useful tool. The fact that the unirradiated lesions have a higher growth rate when a patient is in the hypermetabolic state makes the selection of patients for this method of treatment a matter of great importance. It may also indicate one of the mechanisms of increased radiation sensitivity, since rapidly growing tissue is usually considered to be more radiosensitive.

SUMMARY

1. L-triiodothyronine potentiates the radiation sensitivity of selected local tissues.

2. This drug lends itself to clinical use because of its rapid action at the cellular level.

3. Administration of this drug appears to cause a tumor untreated by roentgen rays to grow more rapidly.

Melvin L. Griem, M.D.
Department of Radiology
Argonne Cancer Research Hospital
University of Chicago
Chicago, Illinois

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THE INFLUENCE OF DELIVERY RATE OF WHOLE BODY 250 KV. ROENTGEN IRRADIATION (30 OR 3 ROENTGENS PER MINUTE) ON MICE, RATS AND GUINEA PIGS*

By MICHAEL P. D'ACQUISTO, MAJOR, MC, *and* EDWARD W. BLACKBURN, CAPTAIN, MSC
WASHINGTON, D.C.

THE influence of delivery rate of whole body irradiation on the $LD_{50(30)}$ has been studied intensively. Tables I and II are a compilation of some of the published data on various species. The discrepancies in the results for mice and rats are apparent. For example, in mice, depending on the report one reads, decreasing rates of whole body irradiation are either more lethal or less lethal. For rats the data are more consistent, but at rates below 10 r/min. the results are conflicting. The monkey appears to be equally sensitive to irradiation at either high or low rates of delivery while the dog is probably a bit less sensitive to low rate exposures. Except for the present report, no information is available on guinea pig response to low rate irradiation.

In the experiment to be reported, three species were studied, the mouse, rat and guinea pig. A ten-fold change in delivery rate of whole body roentgen irradiation was used, 30 r/min. and 3 r/min. In addition to the $LD_{50(30)}$, cumulative mortality, mean survival time and the 72 hour postexposure body weight loss were computed for each species at each of the delivery rates.

PROCEDURE

All animals used were young adult females. In every case, animals of the same species receiving the same total dose, but at the two different rates, were housed together. The entire experiment was performed consecutively; first, mice, then rats and finally guinea pigs. Control animals were kept during the experiment and there was no evidence of disease in them. A total of 390 Walter Reed-Bagg strain mice were used. Their weights ranged between 21–30 gm. Walter Reed-Carworth Farm rats, a total of 180, weighing between 170–220 gm. were used for the rat data. The guinea pig data were contributed by 183 Hartley guinea pigs weighing between 340–440 gm.

In each species the entire group at every dose level was irradiated simultaneously. The rates were either 30 r/min. (29–31 r) or 3 r/min. (2.6–3.3 r) for all three species. All roentgen irradiation was delivered at 250 kv., while the milliamperage and target distance were varied to meet the above rate levels. Inherent filtration was equivalent to 3.2 mm. Be, and filtration of 1.0 mm. Al and 1.0 mm. Cu was added for all exposures. The dose rates were measured in air with a Victoreen chamber at the approximate mid-position of the animal being irradiated.

The animals were observed for 30 days for daily mortality and body weight of survivors. No autopsies were performed. The mean survival time in days of those animals dying in each group was calculated. The 72 hour postirradiation weight loss, expressed as a percentage of the body weight just prior to exposure, was also computed.

RESULTS

Figures 1 to 3 present the 30 day mortality, 72 hour postexposure weight loss and mean survival time versus exposure in each of the three species at the two rates of delivery. Both the mice and rats show quite different responses to roentgen ir-

* From the Division of Nuclear Medicine, Walter Reed Army Institute of Research, Walter Reed Army Medical Center, Washington, D. C.

TABLE I

A COMPILATION OF SOME REPORTED EXPERIMENTAL RESULTS IN MICE AND RATS BASED ON VARYING RATES OF DELIVERY OF RADIATION

Species	Radiation Source	Rate r/min.	Total Dose in Roentgens	Survival Results	Reference No.
Mice	Co^{60}	8–12	—	LD_{50}-750–1,100 r	20
Mice	Co^{60}	.5–.75	—	LD_{50}-1,325 r	
Mice	not stated	30	—	LD_{50}-about 840 r	10
Mice	tantalum	3	—	LD_{50}-1,100–1,200 r	
Mice	Co^{60}	42	—	LD_{50}-772 r	17
Mice	Co^{60}	15	—	LD_{50}-785 r	
Mice	Co^{60}	4	—	LD_{50}-800 r	
Mice	Co^{60}	.5	—	LD_{50}-1,081 r	
Mice	not stated	830	700	66.06% survival—30 da.	7
Mice	not stated	17.2	700	47.8% survival—30 da.	
Mice	not stated	8.6	700	25.0% survival—30 da.	
Rats	250 kv.	34	900	LD_{100} in 14 da.	18
Rats	250 kv.	5	900	survival greater 75%—30 da.	
Rats	250 kv.	6	—	LD_{50}-550 r	2
Rats	1,000 kv.	2.7	—	LD_{50}-970 r	3
Rats	1,000 kv.	550	—	LD_{50}-800–850 r	1
Rats	1,000 kv.	18	—	LD_{50}-just under 800 r	
Rats	1,000 kv.	7.1	850	24% deaths—30 da.	

radiation when given at 30 r/min. in contrast to 3 r/min. (Fig. 1 and 2). In both species, a total exposure that led to death (mice—1,200 r and rats—1,000 r), with survival times of about 5 days, was now reduced to a 100 per cent lethal exposure only after 8–15 days, suggesting a different cause of death. The percentage body weight loss in both mice and rats showed the reduced effects of low rate roentgen irradiation at almost all exposures, as did the mean survival time data. In Table III, the $LD_{50(30)}$ and its 95 per cent confidence limits are listed. The mouse results are just significant at the 95 per cent level while the rat $LD_{50(30)}$ is much increased with low rate roentgen irradiation and is significant well beyond the 95 per cent level as evidenced by the wide spread between the confidence limits. For these two species the results are more encouraging than the data presented in Table 1.

The guinea pig, however, exhibited equal sensitivity to whole body roentgen irradiation regardless of rate of delivery. This failure to respond differently is manifest in all the parameters measured: lethality, weight loss, survival time and $LD_{50(30)}$ (Fig. 3 and Table III).

DISCUSSION

Perhaps too simple an explanation for the species difference reported herein is that there are quite different rates of recovery from roentgen irradiation. It is not clear, however, whether the rate of recovery is dependent in some way on the delivery rate, in addition to species difference. For

TABLE II

A COMPILATION OF SOME REPORTED EXPERIMENTAL RESULTS IN GUINEA PIGS, DOGS AND MONKEYS BASED ON VARYING RATES OF DELIVERY OF RADIATION

Species	Radiation Source	Rate r/min.	Total Dose in Roentgens	Survival Results	Reference No.
Guinea Pig	186 kv.	63	—	estimated LD_{50}—250–300 r	12
Guinea Pig	200 kv.	15.6	200 300 400	50% dead—30 da. 80% dead—30 da. 100% dead—30 da.	6
Guinea Pig	250 kv.	25	300–350	50% dead	15
Dog	1,000 kv.	2.7	—	LD_{50}-about 430 r	3
Dog	2,000 kv.	15	—	LD_{50}-400 r	4
Monkey	250 kv.	3.5	—	LD_{50}-500 r	2
Monkey	250 kv.	3	—	LD_{50}-570 r	8
Monkey	250 kv.	14	—	LD_{50}-600 r	5
Monkey	250 kv.	22	—	LD_{50}-530 r	9
Monkey	250 kv.	23	—	LD_{50}-550 r	16

TABLE III

$LD_{50/30}$ IN MICE, RATS AND GUINEA PIGS

Dose in Roentgens	30 Day Mortality (Deaths/Total)					
	Mice		Rats		Guinea Pigs	
	30 r/min.	3 r/min.	30 r/min.	3 r/min.	30 r/min.	3 r/min.
1,200	20/20	20/20				
1,000	35/35	26/35	15/15	15/15		
770	23/35	15/35	15/15	10/15	10/10	10/10
675	—	—	9/15	4/15	—	—
600	8/35	4/35	10/15	7/15	11/11	12/12
440	2/35	3/35	6/15	0/15	11/12	10/12
350	0/35	0/35	2/15	2/15	6/12	6/12
230	—	—	—	—	3/12	6/12
190	—	—	—	—	2/12	2/12
140	—	—	—	—	1/12	0/12
90	—	—	—	—	0/10	0/10
LD 50(30)*	650	743	498	684	305	287
95% C.L.*	610–694	694–796	448–556	628–743	220–423	222–370

* Miller, L.C., and Tainter, M. L. *Proc. Soc. Exper. Biol. & Med.*, 1944, *57*, 261–264.

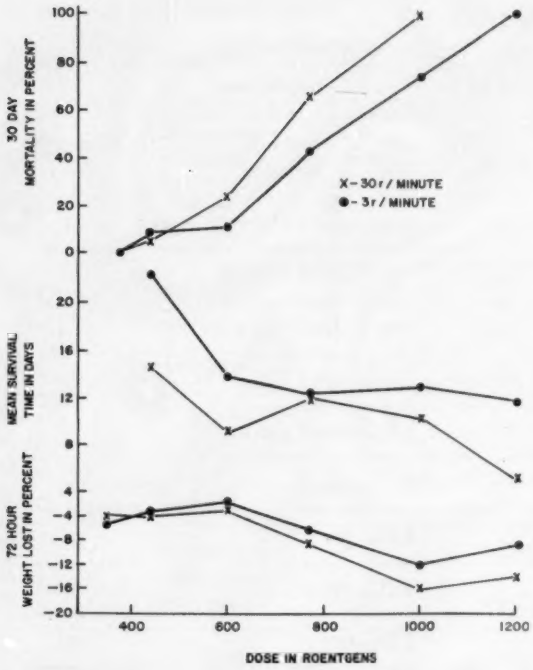

FIG. 1. The response of WR-B adult female mice to whole-body 250 kv. roentgen irradiation delivered at two different rates. Every index measured is improved at the lower rate.

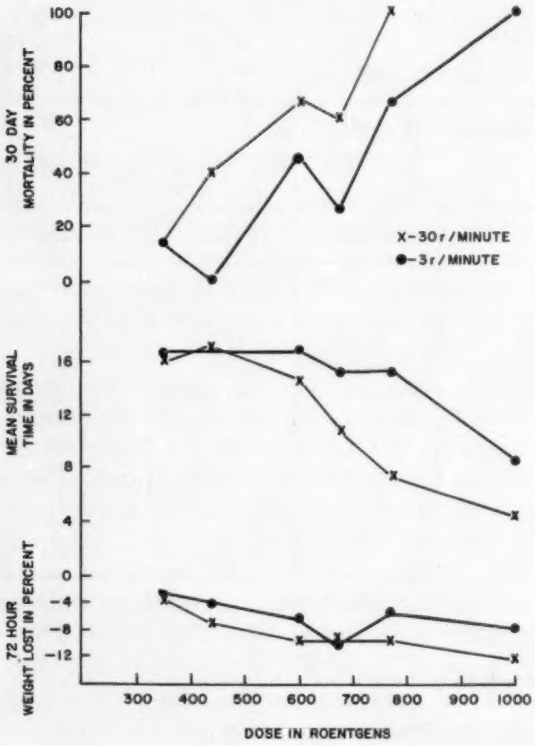

FIG. 2. The response of WR CF young adult female rats to whole body 250 kv. roentgen irradiation delivered at two different rates. Every index measured is improved at the lower rate.

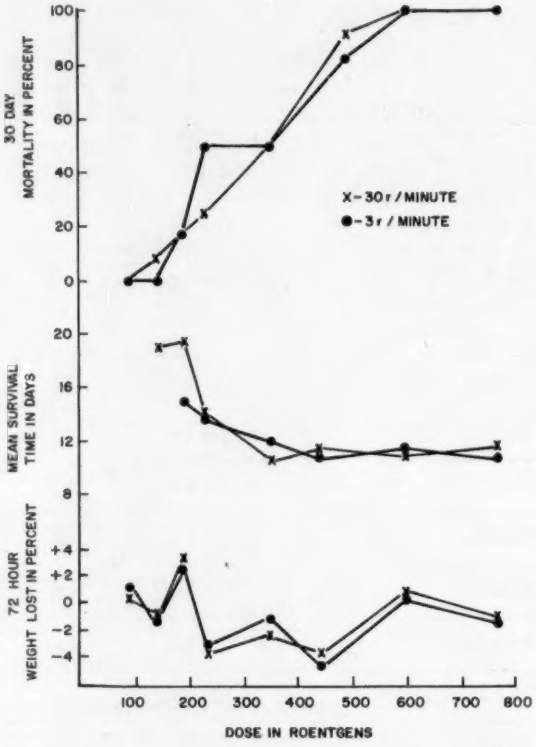

FIG. 3. The response of Hartley young adult female guinea pigs to whole body 250 kv. roentgen irradiation delivered at two different rates. The lack of influence of rate is obvious.

that matter, an explanation for variation in recovery rate among the various species is lacking. The monkey is presumed to show the fastest recovery rate, then the mouse, rat, and finally the guinea pig, in that order.[13,14]

In this experiment, the time intervals for exposure to roentgen irradiation were relatively short, up to 40 minutes for 30 r/min. rate exposures and up to 400 minutes for 3 r/min. exposures. This is not long enough to allow for any significant recovery, as it has been stated that mice have a daily recovery of about 9 per cent and rats 8 per cent.[13] If the roentgen irradiation were delivered over a 24 hour

period, one might expect to see about a 10 per cent improvement in the lethality results due to daily recovery alone. Over a brief 6 hour period, the change should be negligible. However, at 3 r/min. the mouse $LD_{50(30)}$ increases by 14 per cent compared to the $LD_{50(30)}$ at 30 r/min. (743 as against 650 r); rat increase in $LD_{50(30)}$ is 38 per cent at the low rate (684 as against 498 r), while guinea pigs show no change. From the data in Table 1, one may assume that monkeys react as do guinea pigs to delivery rate. Yet the monkey is reported to have the fastest recovery rate and the guinea pig the slowest.[13,14]

It seems obvious that one must look elsewhere for an explanation, as acute recovery information will not allow for extrapolation to response to low rate roentgen irradiation. The increased tolerance to low rate roentgen irradiation in mice and rats is evident at every total dose (Table III) so the increased $LD_{50(30)}$ cannot be attributed to improvement in survival at low doses only. Encouraging is the fact that recovery seems to occur simultaneously with exposure and is not exhausted at even relatively high total doses of roentgen irradiation. Indeed, chronic irradiation studies in mice indicate that, although life span is shortened, death is not due to acute effects.[11,19]

The basic cause for this difference is not known. As far as the three species studied herein are concerned, it is obvious that such things as body weight, life span or the $LD_{50(30)}$ do not correlate with the observed differences in response.

SUMMARY

1. Three species—mouse, rat and guinea pig—were given whole body roentgen irradiation with 250 kv. at rates of 30 r/min. and 3 r/min.

2. The rat showed the most tolerance to low rate roentgen irradiation with an increase of 38 per cent in the $LD_{50(30)}$; the mouse $LD_{50(30)}$ increased 14 per cent, while the guinea pig was equally sensitive regardless of rate.

3. This difference in response cannot be ascribed to accepted acute recovery rates for these species.

Michael P. Dacquisto, Major, MC
Walter Reed Army Institute of Research
Walter Reed Army Medical Center
Washington 12, D. C.

The technical assistance of Raymond Failer and Richard Zaveson is gratefully acknowledged. The illustrations were prepared by the Medical Audio-Visual Department, Walter Reed Army Institute of Research.

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CONTRIBUTION OF PLASMA CONSTITUENTS PRODUCED FOLLOWING WHOLE BODY IRRADIATION ON THE EFFICACY OF LOCAL RADIATION THERAPY*

By MELVIN R. SIKOV, PH.D., *and* JAMES E. LOFSTROM, M.D.
DETROIT, MICHIGAN

A NUMBER of years ago, Hollcroft and her collaborators[2,3,4] demonstrated that the oncolytic effects of local radiation on experimental mouse tumors were increased by concomitantly administering small increments of whole body radiation. They also found that 50 r of systemic exposure was sufficient to elicit a maximum response; larger radiation doses did not bring about any further increase in effect in the two tumors that they studied.

This phenomenon has potential clinical usefulness as well as obvious theoretic importance. We have therefore repeated this work with the two types of tumor used by Hollcroft *et al.* and were able to confirm their findings under different conditions of inoculation and irradiation. We have also extended these studies to other transplantable tumors with a spectrum of other characteristics to determine whether this was a universal phenomenon or was limited to only certain types of tumor.

This work indirectly indicated that the potentiating effect of whole body irradiation might be mediated through some humoral mechanism which was rapidly lost with increasing time between the local and total body exposures. The studies of Edelmann *et al.*,[1] which demonstrated that some toxic material was developed in the serum of rats after whole body irradiation, were also felt to have a bearing on this situation. They have shown that this serum was capable of lowering the LD_{50} of radiation in mice, which may be interpreted as an increase in radiosensitivity. It was found, however, that the serum displayed maximum effectiveness when a period of several days elapsed between irradiation and collection of the blood.

Although the stated differences in time relations existed, it was felt to be of value to investigate the potentialities of blood plasma from irradiated animals *per se*, in increasing the oncolytic effects of tumor radiation. These differences dictated that the effects be studied using plasma obtained at various intervals between irradiation and sacrifice. The results obtained provide some explanation of the mechanisms involved in the whole body synergism as well as indications of their ultimate clinical value.

METHODS

Tumors in active growth, with minimal necrosis, were removed from carrier mice and cut into small fragments. These were implanted subcutaneously into the dorsolateral aspect of the lower thigh of recipient animals, using a modified No. 13 hypodermic needle. After the tumors had attained a suitable size, the experimental mice were divided into 16 groups of 10 or more animals. They were irradiated according to the schedule shown in Table 1 except that doses up to 2,800 r were used for more radioresistant tumors. It is to be noted that within each group the same total tumor dose was administered, the tumor dose being decreased to compensate for each dose of whole body irradiation.

Alternate animals of each experimental group were treated with a Keleket and a

* From the Department of Radiology, Wayne State University College of Medicine, Detroit, Michigan. Work performed under grant from American Cancer Society, supported in part by Receiving Hospital Research Corporation.
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TABLE I

EXPERIMENTAL DESIGN

Whole Body Dose (r)	Local Dose to Tumor (r)			
0	0	800	1,400	2,000
50	0	750	1,350	1,950
100	0	700	1,300	1,900
200	0	600	1,200	1,800
Total Radiation to Tumor (r)	0, 50, 100, 200	800	1,400	2,000

Picker superficial therapy unit.* The radiation was kept localized to the tumor by combined shielding and collimation. Total body irradiation was administered within one minute of the completion of the local exposure, using the same machines with the cone removed.

The tumors were measured in three dimensions with calipers before the initiation of treatment and at frequent intervals thereafter to approximate tumor volume. The tumor size at any subsequent time was expressed in terms of the per cent of the volume at the time of irradiation or PS_o.

$$PS_o = \frac{\text{volume at time } t}{\text{volume at irradiation}} \times 100$$

This was determined for each measurement and group averages were calculated at serial times after irradiation. Each PS_o was compared to the corresponding average for the untreated controls to obtain the per cent inhibition of growth or PI.

$$PI = \frac{PS_o\,(\text{control}) - PS_o\,(\text{experimental})}{PS_o\,(\text{control})} \times 100$$

The amount of inhibition obtained by using various increments of whole body radiation can best be compared with the inhibition obtained with local tumor exposure alone in terms of the per cent enhancement of effect or PE. This was calculated from the maxima of the graphs of per cent inhibition against time after irradiation.

$$PE = \frac{PI\ (\text{no W.B.}) - PI\ (\text{W.B.})}{PI\ (\text{no W.B.})} \times 100$$

In the experiments designed to determine the presence of potentiating substances in the plasma, groups of normal rats were exposed to 1,000 r of total body radiation and exsanguinated at serial times thereafter, ranging from ten minutes through five days. The plasma was separated and injected into mice bearing the Ehrlich carcinoma or the C_3HBA adenocarcinoma immediately after local irradiation of the tumor. The mice were sacrificed after three weeks and the effect evaluated on the basis of the weights of the excised tumors as well as in terms of the per cent inhibition of growth. The Ehrlich carcinoma has also been used for a second study, dealing with the effect of such plasma on survival time and on the production of complete regression of the tumor.

Seven groups of 20 or more mice were used in each experiment. These consisted of untreated controls, mice receiving plasma from unirradiated rats plus tumor irradiation, and 5 groups of mice which received plasma from irradiated rats in addition to tumor irradiation. The results in the groups of mice that received plasma from irradiated animals were compared to those in the group that were identically treated except that the plasma was from untreated rats.

RESULTS

WHOLE BODY IRRADIATION

The effect of administering a portion of the tumor exposure as whole body irradiation has been studied in seven different tumors to date. These results will be presented in detail elsewhere. Three representative tumors will be considered in this report as illustrative of the general findings.

The curves of per cent inhibition of growth have been plotted as a function of time for the L-1 lymphosarcoma, one of the tumors used by Hollcroft *et al.*[2,3,4] and are

* Radiation factors: 120 kv. peak, no filter, half value layer of 1.5 mm. Al. Keleket apparatus: target skin distance, 16 cm., 10 ma., 750 r/min. Picker apparatus: target skin distance, 20 cm., 9.5 ma., 550 r/min.

shown in Figure 1*A*. Much the same results were obtained with the C_3HBA adenocarcinoma, the other tumor that they used. It may be noted that per cent inhibition was markedly increased by administering part of the exposure as total body irradiation for tumor doses of 1,400 and 2,000 r. Essentially the same results were obtained with 50 r that could be produced by higher doses at all tumor dose levels.

As shown in Figure 2*A*, there was essentially no enhancement obtained with 800 r to the tumor. The effect was quite pronounced with total tumor doses of 1,400 or 2,000 r. It is to be noted that the per cent enhancement with a tumor dose of 1,400 r was greater than that obtained with 2,000 r. This relation was seen in many of the other tumors and in the results from the already high per cent inhibition obtained with 2,000 r tumor dose using no whole body component. It is also to be observed that the enhancement was statistically significant at 2,000 r even though the absolute values of per cent enhancement were small.

The effect of whole body irradiation can also be studied in terms of the percentage of the tumors undergoing complete regression or on the basis of increases in the median survival time of the host animals. Cure rate in this tumor (Table II) increased with increasing total tumor dose. A slight generalized increase was seen at 800 r and a more substantial, although still general, increase at 2,000 r. With neither dose was there an increase in regression produced by whole body irradiation as compared to the same total tumor dose without the systemic exposure. At the 1,400 r level, however, there was substantially more regression when any increment of total body radiation was used although this was independent of dose. Median survival times (Table III) were also prolonged by increasing the dose level of tumor radiation, although the addition of total body irradiation had only minimal effects.

The curves of per cent inhibition for the Ehrlich carcinoma (Fig. 1*B*) showed much the same results although the quantitative relations were somewhat altered. In this case, there was a substantial spread between the curves of per cent inhibition at

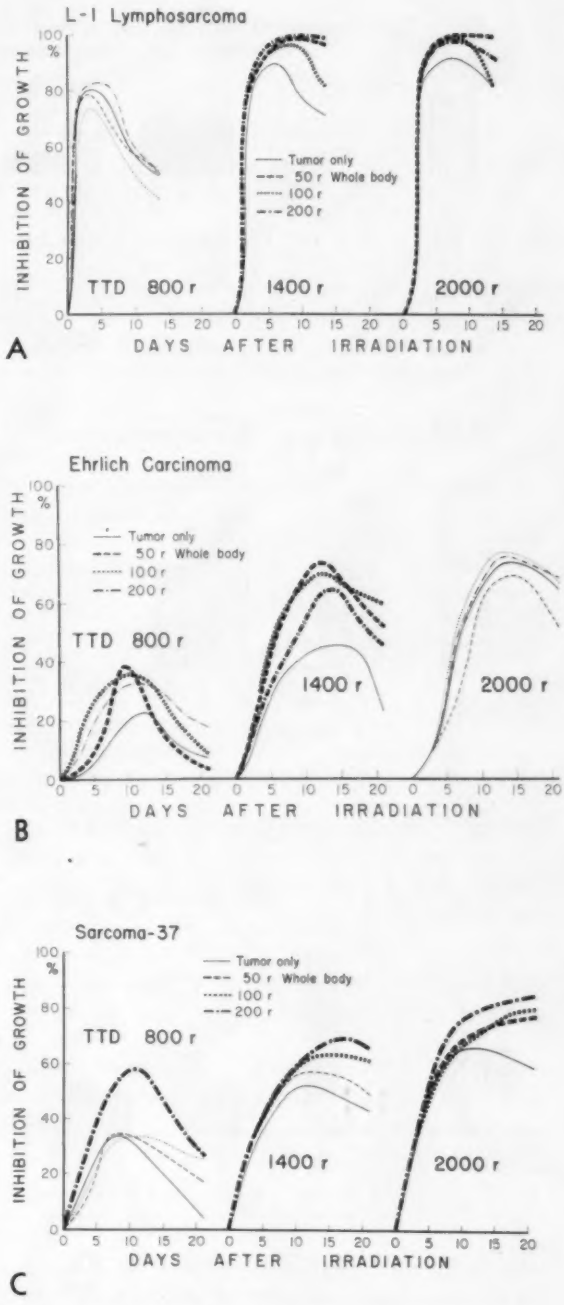
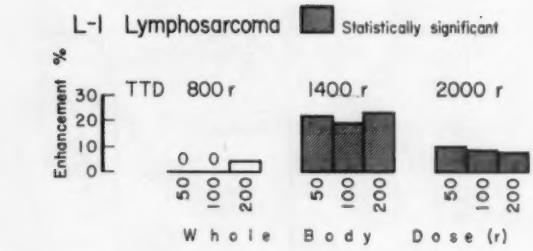


Fig. 1. Per cent inhibition of growth as a function of time after irradiation. Curves are presented for various increments of whole body irradiation at each total tumor dose (TTD). (*A*) L-1 lymphosarcoma, (*B*) Ehrlich carcinoma, (*C*) sarcoma-37.



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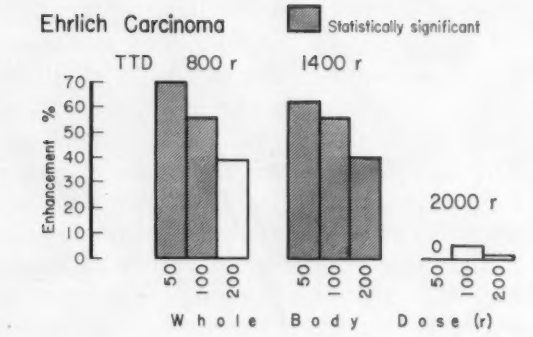
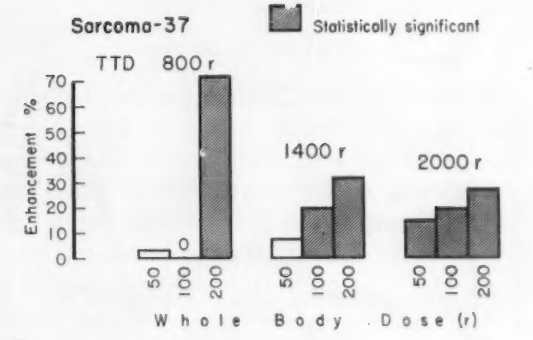


B



C

FIG. 2. Per cent enhancement of effect by increments of whole body irradiation at various total tumor doses (TTD). (*A*) L-1 lymphosarcoma, (*B*) Ehrlich carcinoma, (*C*) sarcoma-37.

tumor doses of 800 or 1,400 r, while at 2,000 r the curves were essentially superimposed. The bar graphs presenting per cent enhancement of effect (Fig. 2*B*) reflected these relations. At the two lower tumor dose levels, enhancement was found to be markedly elevated, whereas at 2,000 r there was essentially no enhancement. There was much the same amount of enhancement at all whole body dose levels. However, a possible tendency toward decreased effect with increasing whole body dose was noted.

With the Ehrlich tumor (Table II) there were essentially no animals with complete regression at any tumor dose level when it was not accompanied by systemic exposure. At 1,400 or 2,000 r, however, total body irradiation substantially increased the percentage of complete regressions of the tumors. This was largely independent of the specific whole body dose used. Whole body exposure had only minimal effect on the median survival times with this tumor.

Many of the other tumors studied showed results similar to those of the L-1 lymphosarcoma and the Ehrlich carcinoma. Some tumors, such as the Sarcoma-37, on the other hand (Fig. 1*C*), showed a tendency toward progression of per cent inhibition with increasing whole body dose. Per cent enhancement (Fig. 2*C*) also showed this linear increase with increase in the fraction of the radiation administered systemically. As shown in Tables II and III, whole body irradiation did not affect the survival time nor increase the percentage of animals in which the tumor regressed completely.

PLASMA ADMINISTRATION

As may be seen in Figure 3, the administration of plasma from previously irradiated rats did not increase the per cent inhibition of growth above that obtained with plasma from untreated animals. When the effect of plasma injection is considered in terms of the effect on tumor weight at sacrifice, a somewhat different relation is seen (Fig. 4). It will be noted that tumor weight was significantly reduced in animals receiving plasma obtained at either one or three days after irradiation as compared to the weight of tumors from animals that received untreated plasma. The tumor weight was also decreased when plasma ob-

TABLE II

PER CENT OF MICE WITH COMPLETE REGRESSION OF TUMORS

Whole Body Dose (r)	Total Tumor Dose (r)											
	0	800	1,400	2,000	0	800	1,400	2,000	0	800	1,400	2,000
0	0	20	40	80	0	0	0	10	0	15	14	29
50	0	30	80	100	0	10	30	10	7	27	7	46
100	0	20	90	100	0	0	22	38	8	7	22	25
200	0	10	90	90	0	0	25	30	13	23	27	58
	L-1 Lymphosarcoma				Ehrlich Carcinoma				Sarcoma-37			

TABLE III

MEDIAN SURVIVAL TIMES

Whole Body Dose (r)	Total Tumor Dose (r)											
	0	800	1,400	2,000	0	800	1,400	2,000	0	800	1,400	2,000
0	14	19	20	21	35	30	34	44	14	22	19	25
50	14	17	24	24	26	37	46	42	14	21	19	30
100	14	16	22	19	27	33	41	52	17	21	22	27
200	14	18	24	25	26	41	41	40	14	20	29	31
	L-1 Lymphosarcoma				Ehrlich Carcinoma				Sarcoma-37			

tained ten minutes after irradiation was injected, although this was not statistically significant.

It was also found (Fig. 4) that the median survival times as well as the percentage of the animals showing complete regression of the tumor were appreciably increased after the injection of plasma obtained at any time after irradiation beyond ten minutes.

Per cent inhibition of growth in the C_3HBA tumor (Fig. 5) showed a statistically significant increase in mice which were injected with plasma obtained at ten minutes, one day, or five days after irradia-

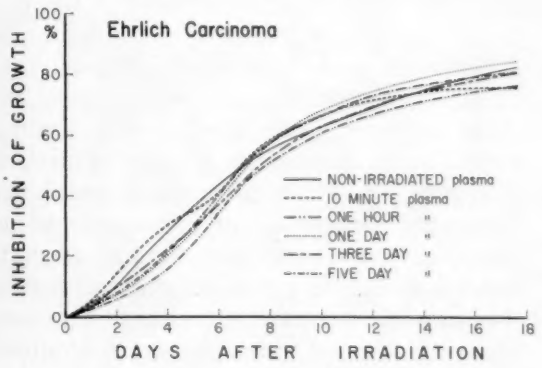


FIG. 3. Per cent inhibition of growth for the Ehrlich carcinoma after 2,000 r tumor radiation as influenced by the injection of plasma from previously irradiated animals.

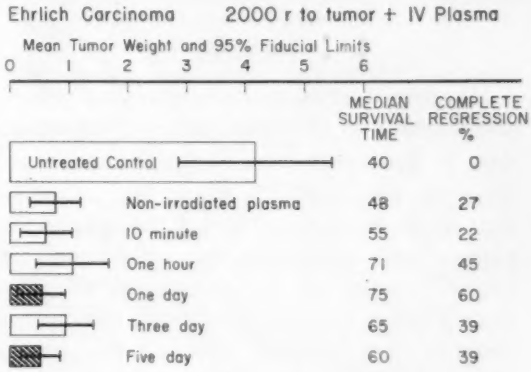

Ehrlich Carcinoma 2000 r to tumor + IV Plasma
Mean Tumor Weight and 95% Fiducial Limits
0 1 2 3 4 5 6
MEDIAN SURVIVAL TIME
COMPLETE REGRESSION %
Untreated Control 40 0
Non-irradiated plasma 48 27
10 minute 55 22
One hour 71 45
One day 75 60
Three day 65 39
Five day 60 39

FIG. 4. Mean tumor weight at sacrifice, median survival time, and per cent of animals showing complete tumor regression after 2,000 r to the Ehrlich carcinoma as influenced by the injection of plasma from previously irradiated animals.

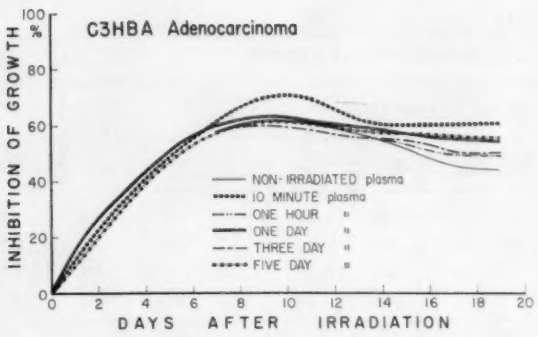


FIG. 5. Per cent inhibition of growth for the C_3HBA adenocarcinoma after 2,200 r tumor radiation as influenced by the injection of plasma from previously irradiated animals.

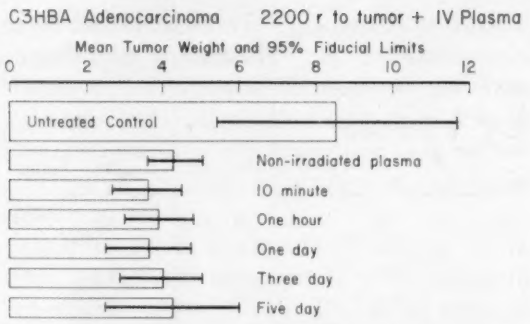


FIG. 6. Mean tumor weight at sacrifice after 2,200 r to the C_3HBA adenocarcinoma as influenced by the injection of plasma from previously irradiated animals.

tion. The potentiating effects with plasma from animals exsanguinated at one hour or three days after irradiation were somewhat less pronounced and were not statistically significant.

Mean tumor weights at sacrifice (Fig. 6) were substantially smaller in cases where injection with plasma obtained at either ten minutes or one day after irradiation was made, in agreement with the findings in terms of inhibition. These decreases were not, however, statistically significant. In instances where injections were made five days after irradiation, an effect in terms of inhibition was noted but not a corresponding decrease in tumor weight, although the variability in this group was sufficiently great to mask any changes.

DISCUSSION

It is apparent that the results of the work of Hollcroft *et al.*[2,3,4] are readily reproducible. It is further found that the increased oncolysis produced by whole body irradiation is neither a function of the site of implantation of the tumor nor of the method of administration of the radiation, since we were able to make pronounced changes in these factors without altering the results obtained. This enhancement was found to occur in all of the tumors studied, although it was more pronounced in some than others. Likewise, the amount of whole body radiation required for maximal effect was somewhat variable from tumor to tumor. In most cases, however, 50 r of systemic exposure was sufficient to elicit maximum enhancement of effect, as was reported by Hollcroft and Matthews.[4]

The results reported after the injection of plasma are not as conclusive as might be desired. They are sufficient to demonstrate, however, that the increased oncolysis produced by whole body exposure can be simulated by administering plasma from previously irradiated animals together with the local irradiation. Further experiments have been performed on the enhancement of effect by the injection of plasma since the time that this manuscript was prepared. These studies have yielded confirmation of the results here presented. It has also been found that the magnitude of this phenomenon is highly dependent on the tumor dose used.

Hollcroft and Matthews[4] studied the effect of preventing the interchange of blood between body and tumor during whole body irradiation and investigated the results of variations in the interval between the total body and tumor irradiation. They concluded from the former that the radiation effect was instantaneous and that some factor must interchange between the body and the tumor for the synergism to occur. The latter experiments demonstrated that the magnitude of the synergism decreased with increasing time between the two exposures.

The injection of plasma from rats exsanguinated at ten minutes after irradiation is essentially comparable to the conditions pertaining in our whole body irradiation experiments. Since this plasma was seen to act synergistically, we may conclude that the enhancement of oncolysis by whole body irradiation is mediated via some substance contained in the plasma. Support is lent to this contention by the fact that plasma obtained at one hour after irradiation was uniformly without potentiating effect.

It is not possible to offer an explanation of the mechanisms or to identify the substance involved on the basis of the present experiments. The immediacy of the reaction leads us to implicate some hormonal mechanism, perhaps adrenal, although firm evidence is lacking.

As was discussed above, there is no synergism when long intervals intervene between the local and the total body irradiation. On this basis it is somewhat unexpected that plasma from animals exsanguinated at one or more days after irradiation is effective in potentiating the effect of tumor irradiation. Since the effects of whole body irradiation have not been evaluated with intervals of greater than twenty-four hours between exposures, this finding is not as contradictory as it might seem. It would, however, lead to the supposition that some different mechanism or substance develops with longer intervals between whole body irradiation and sacrifice. It further raises the possibility that there are two distinct mechanisms or substances operating in the whole body potentiation of radiation effect. Further experimental work would be required, of course, to evaluate this consideration. The reported experiments offer no indications as to the nature of this second substance, if it in fact does exist. The possibility of some immunologic reaction obviously suggests itself and will be investigated in the near future.

SUMMARY

The amount of oncolysis produced by localized roentgen irradiation can be substantially increased by administering a small increment of the tumor dose as whole body irradiation. The exact quantitative relations between the doses for local and systemic exposures were found to be quite complex although 50 r of total body irradiation was often sufficient to elicit maximum effect. This increased oncolysis can be partially simulated by administering plasma from previously irradiated animals together with irradiation of the tumor. This was interpreted as indicating that some substance or substances are present in the plasma following total body irradiation which may be involved in the synergism.

Melvin R. Sikov, Ph.D.
Wayne State University
College of Medicine
1401 Rivard Street
Detroit 7, Michigan

The authors wish to express their appreciation to Miss B. B. Cook and Mr. F. B. Norris for their technical assistance.

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ISODOSE CURVES ABOUT THE BEDS OF PATIENTS CONTAINING INTRACAVITARY RADIUM OR COBALT 60 SOURCES*

By WILLIAM F. BARRY, Jr., M.D.,† *and* RONALD KRUEGER, B.S.‡
DURHAM, NORTH CAROLINA

DESPITE the fact that every institution has "radium precautions" for personnel working near radioactive patients on the wards, we could find only one article in the literature on this subject.[3] Therefore, we began to develop a set of data which would guide the radiologist in setting up adequate radiation precautions.

We first measured the radiation at the head of the bed, the foot of the bed, both sides of the bed, 4.3 cm. above the sternum and 4.3 cm. above the symphysis pubis. Table 1 is a tabulation of these data from which one interesting observation can be made. The point above the symphysis was a rather "hot spot." This is a logical observation, but it is this point at which the hands are held when irrigating a catheter, checking pads for bleeding, checking the position of sources, adjusting T binders and manipulating bed pans. Using the lowest reading we obtained (1,000 mr/hr.), it would be possible to receive the weekly maximum permissible dose of irradiation to the hands in ninety minutes.[2] Any nurse could receive this amount in 3 or 4 tours of duty. The max. exposure (2,500 mr/hr.) would produce the same dose in thirty-six minutes.

TABLE I

BEDSIDE MONITOR READINGS (mr/hr.)*

	Highest	Lowest	Average
Side	300	60	147
Foot	50	10	26.5
Head	100	15	34.5
Sternum	300	50	175
Pubis	2,500	1,000	1,746

* Average readings of 22 patients corrected to the equivalent of 64 mc Co^{60}.

We then developed isodose curves, using both patients and a wax phantom shaped like a patient. The shape of our radium curves agrees very closely with those of Walstam.[3] Also, our isodose curves measured about a phantom containing various intensities of radium and cobalt 60 agree in shape with similar curves about different-size patients containing different intensities of cobalt 60 (Fig. 1). Our curves do not agree in shape or intensity with the data published in NBS Handbook 54. Figure 2 shows a comparison of measured curves with those calculated from Handbook 54 data. This is to be expected as the National Bureau of Standards data were derived from the inverse square law.[1] Figure 3 is a logarithmic plot of measured readings and inverse square law calculations of the same intensity source. There is a difference in intensity and slope of the curves which we believe is due to the absorption coefficient of the phantom material and human tissue.

The curves as presented can be used by any institution having a calibrated rate meter. By accurately measuring any point on the curves, intensity values can be established for any individual patient. Thus, radiation dose rates may be determined for any area in the room. These curves may also be used in the teaching of ward personnel who are around such patients.

RECOMMENDATIONS

As a result of our observations, we would like to make the following recommendations in regard to radiation precautions around patients containing intrauterine or vaginal radiation sources.

* This project was supported by a grant from the United Medical Research Foundation of North Carolina.
† Associate Professor of Radiology, Duke University Medical Center, Durham, North Carolina.
‡ Research Technician, Duke University Medical Center, Durham, North Carolina.

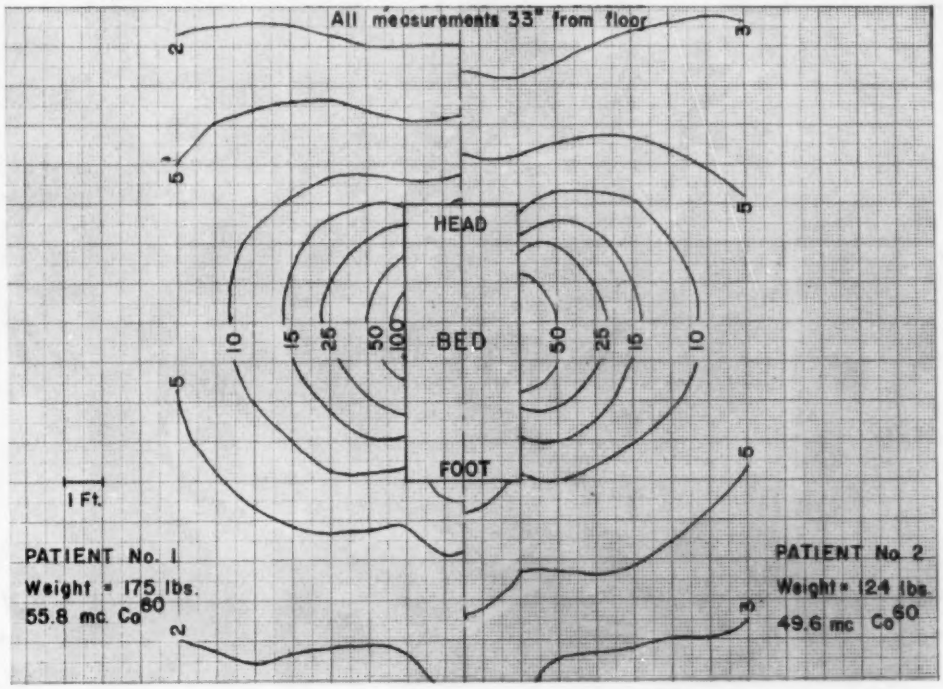

Fig. 1. Isodose curves about the beds of 2 patients, containing 55.8 mc and 49.6 mc Co^{60}, respectively.

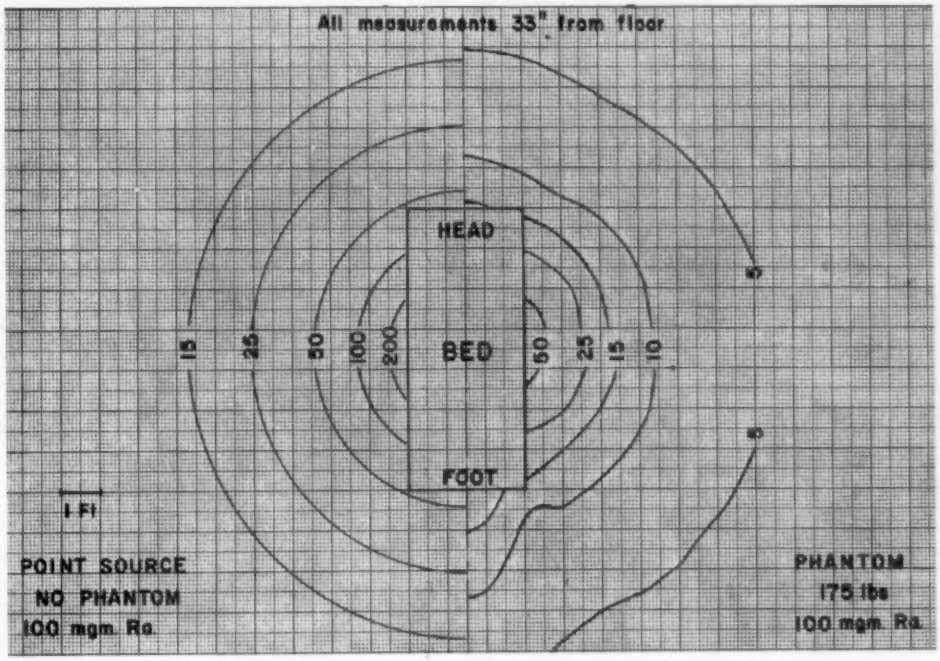

Fig. 2. Dosimetry curves for 100 mgm. radium.

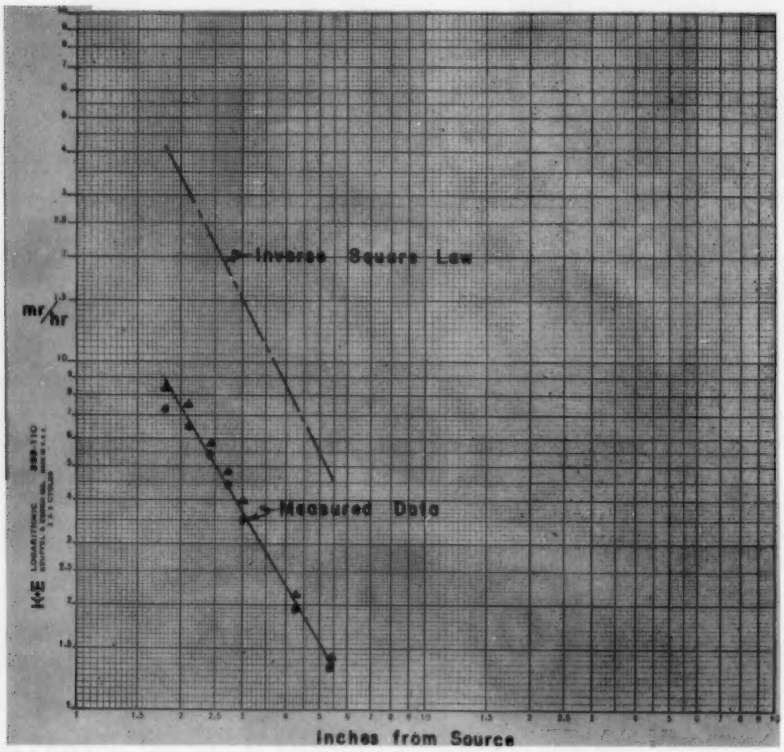

FIG. 3. Logarithmic plot of measured readings and inverse square law calculations of a 64 mc Co^{60} source in a 175 lb. phantom.

1. The foot of the bed should be placed against the wall.
2. As little time as necessary should be spent near the patient's pubis.
3. All catheter handling should be done with an extension tube in place.
4. When it is necessary to be near the bedside, one should stand as near the head of the bed as possible.
5. Visitors should be encouraged to sit near the head of the bed and to make the visits as short as possible.
6. Unnecessary visiting should be discouraged, particularly among those of childbearing age.
7. Pregnant patients should not be allowed in the vicinity of these patients.

William F. Barry, Jr., M.D.
Department of Radiology
Duke University Medical Center
Durham, North Carolina

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RADIATION ACCIDENTS*

By EUGENE L. SAENGER, M.D.
CINCINNATI, OHIO

WITH the rapid growth of the use of nuclear technology in science, industry and national defense, there is an increasing likelihood of serious radiation accidents. Since the radiologist is intimately concerned with the effects of ionizing radiation, both on humans and the environment, he may well be called on as an active participant or consultant in many aspects of such accidents.

Our interest in radiation accidents began in 1951 when a radium spill of 50 mg. occurred in Cincinnati.[15] A review of this situation demonstrated that there was much lost motion in handling the many problems which arose. Most of the procedural errors were due to absence of a preexisting plan. The most helpful techniques devised could be carried out simply and were more the exercise of common sense than the application of involved or esoteric bits of scientific information. Therefore, in the past two years with the active help of many experienced individuals throughout the United States, we have been engaged in the preparation of a handbook on medical aspects of radiation accidents, which will be completed shortly. The present report summarizes some of the highlights of this study.

There is a wealth of information on various types of radiation accidents in the medical and scientific literature beginning about 1952 and increasing steadily since then. These accidents include a great variety of external total and partial body exposures, contamination of body surfaces and internal exposures following ingestion and inhalation of radioactive materials and fixation of radionuclides in the body. A summary of the experiences of the Atomic Energy Commission compiled from several reports by Hayes[7] is presented in Table 1. There has been a total of only 77 incidents, in spite of an enormous increase in size of the total program, in a thirteen year survey. The data of this paper exclude all consequences of nuclear weapon damage at Hiroshima and Nagasaki. Some of the experiences resulting from radioactive fallout in the Marshall Islands[2] following the planned explosion of a thermonuclear weapon will be utilized. There have been only 3 radiation deaths in the United States, and 1 following the Yugoslavian criticality accident. The chronology of serious radiation accidents resulting in relatively high doses of external radiation is summarized in Table II.[16] Particularly complete reviews of external radiation exposures resulting in the acute radiation syndrome have been published by Hempelmann *et al.*,[8] Gerstner,[5] Howland and Warren,[9] and Thoma and Wald.[17]

TABLE I

AEC RADIATION ACCIDENTS (1945–1958)

Criticality Incidents	11
Reactor Incidents	9
Contamination	21
Fires	12
Explosions	4
Transportation	6
External Personnel Exposure	14
Total	77

At present, a radiation accident may be defined as an unforeseen occurrence, either actual or suspected, involving exposure to, and contamination on or within, humans and the environment by radiation. The accident will be considered as occurring with-

* From the Radioisotope Laboratory and Department of Radiology, University of Cincinnati, College of Medicine.
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TABLE II

CHRONOLOGY OF SEVERE RADIATION ACCIDENTS

Accident	Date	No. of Individuals	Type
Los Alamos I	8–21–45	2	Criticality (experimental assembly)
Los Alamos II	5–21–46	8	Criticality (experimental assembly)
Argonne	6–2–52	4	Criticality (reactor)
U.S.S.R.	1953–54?	2	Criticality (reactor)
Oak Ridge	6–16–58	8	Criticality (processing)
Yugoslavia	10–15–58	6	Criticality (reactor)
Los Alamos III	12–30–58	2	Criticality (processing)

in a short time period of seconds to days. Chronic occupational or other long term exposures are not considered.

TYPES OF ACCIDENTS

With the many different sources of radiation, the types of accidents can be quite varied. There are basically two types: (1) exposure to an external source; and (2) contamination on or within the body by radioactive materials. These two major types of exposure may of course be combined. The principal sources of radiation and the types of accidents which can occur are shown in Table III. Types of potential accidents associated with fissionable materials are varied. Major accidents listed in Table II are all of the criticality type, although some occurred in experimental critical assemblies, some in reactors and others in processing plants. The characteristics of fissionable material vary with the mass and shape of the material. A system containing fissionable material becomes critical when the number of neutrons produced in the system equals those lost by leakage and capture. If conditions of self-sustained criticality are exceeded, a chain reaction will occur with production of varying amounts of fast neutrons and gamma rays. Reactors may also release large quantities of radionuclides as demonstrated in the Windscale accident.[1] Contamination is the major problem associated with fuel element manufacture. The external hazards are usually minimal as long as critical configurations are avoided. In fuel element reprocessing in order to reclaim the remaining fissionable material, the external hazard becomes significant because of the presence of large quantities of fission products. In this situation the contamination problem is also serious. Sealed sources when intact are only an external hazard but all sources can leak under certain conditions; the hazard produced depends on the radionuclide

TABLE III

TYPES OF ACCIDENTS WHICH CAN OCCUR

Source	External Radiation	Radioisotope Contamination	Mixed
Critical Assembly	yes	minimal	yes
Reactor	yes	yes	yes
Fuel Element Manufacture	yes	yes	yes
Fuel Element Reprocessing	yes	yes	yes
Radioisotope Manufacture, Processing, Use	yes	yes	yes
Sealed Sources (intact)	yes	no	no
Sealed Sources (leaking)	yes	yes	yes
Particle Accelerators	yes	yes	yes
Roentgen-Ray Generators	yes	no	no

used. In regard to all types of particle accelerators, the radioisotope hazard is produced by the targets or other components irradiated by neutrons or other high energy particles.

In most radiation accidents there have usually been significant human mistakes often contributing to the accidents and impeding their handling. The causative aspect is that there is a failure of communication between individuals, leading to easily discernible departures from well-accepted and previously well-tested, safe procedural routines. Once the accident cycle has begun, many human beings panic, in spite of being well trained, and behave most irrationally. Such behavior and its consequences should be anticipated in these accidents.

A simple emergency plan anticipating all possible accidents for the radiation sources utilized should be adopted well in advance of such unpleasant experiences. If the operating personnel is then well disciplined in activating such an emergency plan, the consequences of such accidents can be greatly minimized. A very simple emergency procedure applicable to a wide variety of such events is presented in Table IV. This procedure can be modified for industrial installations, research laboratories or hospitals depending on the hazards encountered.

THE ACUTE RADIATION SYNDROME

DOSIMETRY

The proper care of humans in any accident depends upon many factors but principally on a clear understanding of the acute radiation syndrome. If one were immediately able to carry out a simple laboratory test which would produce an accurate estimate of the dose received, the entire problem would be greatly simplified. No such test is presently available. The film badges and personnel dosimeters usually employed may well be too sensitive for the high doses encountered. In several accidents no film badges or dosimeters were in use, since criticality accidents had not been considered as likely possibilities.

Dosimetry continues to be a very difficult problem. The radiation produced is usually mixed and may include gamma rays, neutrons, alpha and beta particles. There is often "poor geometry" from the external source, *i.e.*, an extended source with the exposed individual close to it so that the relative precision used in radiation therapy cannot be achieved. The relative biologic effectiveness (RBE) of these radiations is not well understood for conditions of lethality and morbidity for man. One must realize that an RBE determined for genetic purposes in an animal may be unrelated to the RBE for death or sickness in

TABLE IV

EMERGENCY PROCEDURES FOR RADIATION ACCIDENTS

1. Evacuate possibly exposed personnel from accident area and give first aid
2. Notify Medical Phone_____
   Health Physics (Industrial Hygiene) Phone_____
   Management Phone_____
3. Close off radiation area. Turn off air conditioners. Seal area if contamination is likely
4. Confine and survey all contaminated people
5. Evaluate situation in regard to
   a. Contamination by radioactive isotopes
   b. Neutron exposure
   c. Level of radiation exposure
6. If contamination is present, perform simple decontamination and resurvey patient
7. Put patient in bed. Do brief physical examination
8. Save all samples of clothes, blood, urine, stool, vomitus. Label with name, time, date
9. Do routine blood cell counts
10. Obtain careful history of accident
11. Send patient to hospital if exposure of 100–250 rad or more is suspected

man. The rem has been used frequently in the past but tends to be somewhat misleading for several reasons. In many exposures involving neutrons, it is difficult to assign a correct RBE for the neutron dose. The energy spectrum of the neutrons is sometimes not known. Therefore, the absorbed dose should be described in rad rather than rem.

The dose due to neutrons can be estimated by calculations based on the assay of radioactive sodium (Na^{24}) which is produced by interaction of neutrons with stable sodium (Na^{23}) in the body. If the spectral distribution of neutrons can be tested for a situation similar to that producing the accident, one can then evaluate the neutron contribution.[10] It is sometimes necessary to reconstruct the accident situation in order to estimate the doses, although such measures are difficult, time consuming and expensive.

If area monitors, other personnel dosimeters and area neutron detectors are available, the determination of dose becomes more accurate. In most situations, several days or even weeks may transpire before the dose calculations are available. In order to arrive at a relatively precise estimate of dose one should investigate the following parameters:

I. External radiation
  A. Gamma dose
    1. Dose in rad
    2. Energy
  B. Neutron dose
    1. Na^{24} activity of body, blood, urine, whole body counter
    2. Neutron/gamma ratio
    3. Neutron spectrum
  C. Beta particle dose
II. Radionuclide contamination
  A. Elements present
  B. Physical form—particulate, gas, vapor, etc.
  C. Chemical form—solubility, reactivity
  D. Route of incorporation into body
    1. Ingestion
    2. Inhalation
    3. Skin—intact or through wounds
  E. Metabolic path in body

CLINICAL MANIFESTATIONS

Since physical data are often not available, in order to assign exposed patients to dose groups it is necessary to correlate the clinical manifestations and laboratory data in an attempt to foretell the clinical course. The observations of radiation therapy, radiation accidents and atomic bombing reveal a relatively clearcut complex of symptoms in spite of the great variation in types of exposure and patients exposed. These observations have been very clearly discussed by Gerstner[5,6] and by Thoma and Wald[17] and the following material is derived from their studies.

When man is exposed to a single acute whole-body dose of ionizing radiation, a characteristic syndrome develops which is roughly related to the dose received and the sensitivity of the individual patient. The radiation syndrome can be divided clinically into five groups as shown in Table v. There are slight differences in the classification used by Gerstner as compared to that of Thoma and Wald. Thoma and Wald have developed interesting methods of scoring clinical laboratory tests to aid in recognition and classification of the stage of the acute radiation syndrome in a given patient. Since the interpretation of the multitude of symptoms, signs and laboratory studies in such individuals can become most confusing, it would be worthwhile to retain this classification in dealing with the acute radiation syndrome in the future. Each individual who has written on the subject has used a somewhat different classification and standardization; therefore, general adoption of this classification would now become valuable.

The acute radiation syndrome is conveniently divided into four stages as follows: (1) initial or prodromal stage (eight to forty-eight hours' duration); (2) latent stage (two to three weeks); (3) manifest illness stage (two or three to six weeks); and (4) recovery stage (eight to fifteen weeks).

The prodromal findings include anorexia, nausea, vomiting, extreme sweating, fatigue and prostration. If the onset of these

TABLE V

CLINICAL RADIATION INJURY GROUPS

Group No.	Clinical Manifestations	Dose Classification	
		Thoma and Wald*	Gerstner†
I	Mostly asymptomatic; occasional minimal prodromal symptoms	10–160 rad	51–100 r 101–150 r
II	Mild form of acute radiation syndrome; transient prodromal nausea and vomiting; mild laboratory and clinical evidence of hematopoietic derangement	200–400 rad	150–400 r Hematopoietic
III	A serious course; severe hematopoietic complications, and some evidence of gastroenteric damage present in upper portion of group	400–600 rad (297+)	401–600 r Hematopoietic
IV	An accelerated version of acute radiation syndrome; gastroenteric complications dominate clinical picture; severity of hematopoietic complications is related to survival time after exposure	600–1,400 rad	Gastrointestinal
V	A fulminating course with marked central nervous system impairment	1,500–10,000 rad	Cerebral

* Dose in rad according to approximate ranges in Table III of Thoma and Wald.[17]

† Approximate dose in r from Table III and section entitled "Dependency of Acute Radiation Syndrome on Air Dose" of Gerstner's paper.[6] These doses are expressed as air dose, *i.e.*, exposure dose, and are thus in terms of roentgens.

symptoms is within a few minutes after exposure and they rapidly worsen over the next few days, a fulminating course can be anticipated. If there is improvement within several hours or onset after several hours, a milder course can be expected. These symptoms are, of course, rather nonspecific and can easily be induced by panic and apprehension. If several individuals are involved in an accident, it is helpful to separate and isolate them if suitable facilities are available or can be improvised. The more highly educated the patient, the more likely he is to be apprehensive because he can anticipate his clinical course. Thus, in a group, proper evaluation of prodromal symptoms can become meaningless.

The presence of diarrhea in the prodromal period is a serious sign occurring in patients in Groups IV and V, all of whom died. It appeared on the fourth day in 2 patients and within forty-five minutes in 1 patient who received a massive dose and died in thirty-six hours. Weakness and fatigue occurred occasionally in Groups I and II but were severe in all other groups. Other symptoms present in Groups III, IV and V included conjunctivitis, erythema, sweating and paresthesias. Oliguria was present in 2 patients, both of whom died. Immediate central nervous system symptoms were manifested only by the 1 patient in Group V who showed ataxia, disorientation and cardiovascular collapse. He then became comatose, dying in thirty-six hours. Dose estimates were 9,200 rad and 12,000 rem.

During the latent stage, these symptoms remit and there is a feeling of well-being. The patient is asymptomatic and often feels able to work. The length of this stage is somewhat dependent on the dose received. In 2 Los Alamos patients who died,[8] the latent period terminated at about ten and six days, respectively. In the Yugoslavian fatality, the latent period lasted about three weeks except for epilation

which began on the fourteenth day.

The stage of manifest illness begins somewhat abruptly about the eighteenth to twenty-first day, although some signs are found as early as fourteen days. Principal findings include fever, overt or occult infections, scalp hyperesthesia and epilation, purpura and hemorrhage, diarrhea, ileus, cardiovascular collapse, severe lethargy and changes in sensorium. Patients in Group I showed no significant findings of manifest illness. Weakness and marked fatigue occurred in all other patients. In Group II patients these findings occurred at five to six weeks. In Group III they occurred immediately. These symptoms lasted for several months.

Epilation began from thirteen to twenty days but in most patients it began at sixteen to eighteen days. The patient who died at one and one-half days and 1 who died at nine days showed no epilation. Sporadic episodes of fever were observed in half of the patients in Group II and in all patients above that group, being of short duration in Group II and lasting one or more weeks in the more severe cases. Clinical evidence of infection was found in half of Group II patients and all Group III patients. Definite clinical infection was not found in the Group IV or V patients, all of whom died. Hemorrhagic phenomena such as gingival bleeding, epistaxis, petechiae and purpura were observed in most cases in Group II and above who survived beyond the third week. Serious hemorrhage occurred in 2 patients in the fourth week. One, a Yugoslavian woman with 1,024 rem (500 rad), had menorrhagia and another, a Yugoslavian man with 840 rem (640 rad), died with uncontrollable hematemesis and hemoptysis.

In Group III and above, recurrent anorexia, nausea, abdominal discomfort, prostration and oliguria appeared at the peak of manifest illness. They occurred earlier in more acutely ill patients who also had vomiting, diarrhea, and abdominal distention. Disorientation, shock, coma and death followed in several instances. Jaundice was transient in 2 patients in Group III and became marked terminally in the 2 Group IV patients. Weight loss was mild in Group II and more severe in Group III. A helpful clinical flow sheet[17] of symptoms and signs is shown in Figure 1. This diagram is useful in clinical evaluation. Careful daily physical examinations and recording of exact times of new clinical observations are essential for proper handling of these patients. If laboratory aids are lacking but physical dose estimates are available, the curves of Figure 2[6] may be used to determine needed hospital facilities, if large numbers of individuals are involved.

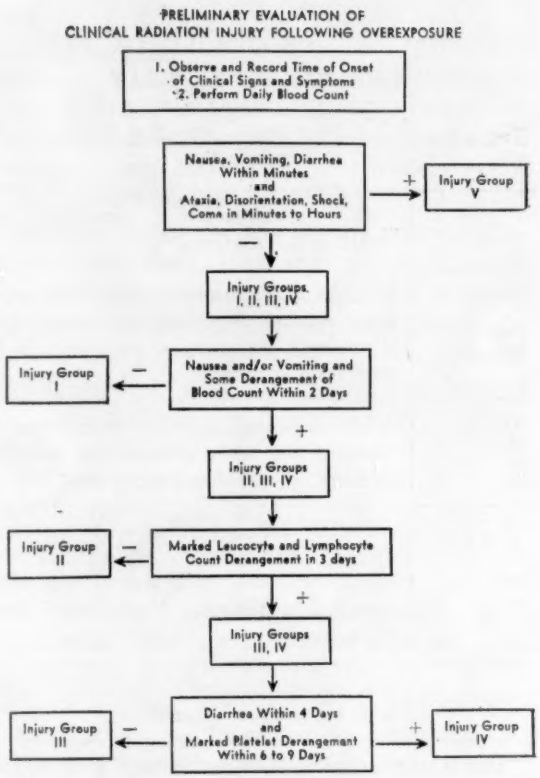
PRELIMINARY EVALUATION OF
CLINICAL RADIATION INJURY FOLLOWING OVEREXPOSURE
1. Observe and Record Time of Onset of Clinical Signs and Symptoms
2. Perform Daily Blood Count
Nausea, Vomiting, Diarrhea Within Minutes and Ataxia, Disorientation, Shock, Coma in Minutes to Hours
+
Injury Group V
−
Injury Groups I, II, III, IV
Injury Group I
−
Nausea and/or Vomiting and Some Derangement of Blood Count Within 2 Days
+
Injury Groups II, III, IV
Injury Group II
−
Marked Leucocyte and Lymphocyte Count Derangement in 3 days
+
Injury Groups III, IV
Injury Group III
−
Diarrhea Within 4 Days and Marked Platelet Derangement Within 6 to 9 Days
+
Injury Group IV

Fig. 1. This flow sheet can be utilized for the rapid sorting of patients into injury groups so that proper follow-up and therapy can be expeditiously instituted.[17] (Reproduced by permission from the *Journal of Occupational Medicine*.)

Laboratory Studies

There have been a great number of laboratory tests performed in the investigation of this syndrome. Most have been done as

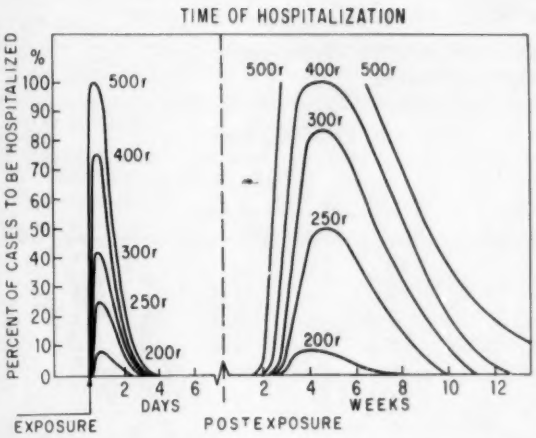

Fig. 2. Estimate of incidence and duration of hospitalization for populations exposed to various amounts of penetrating ionizing radiation.[6] Doses given as roentgens in air. For example, assuming that a population was exposed to 250 r, about 25 per cent would require hospitalization during the first two days after exposure. The large influx of patients could be expected in about two to three weeks after exposure.

aids in clinical handling of the patient; some have been performed essentially for research purposes. Since most physicians have not had personal experience in handling such cases, it is essential that the laboratory studies be properly organized to yield the maximum information with as little discomfort as possible to the patient. Thoma and Wald[17] have organized these procedures in a relatively simple manner to accomplish these purposes.

In order to utilize the many individual data which were obtained in 32 patients in the seven accidents listed in Table II, it was first necessary to determine normal values for the techniques used and then to assign rank numbers to significant deviations from these normal values. Hemoglobin, erythrocytes, hematocrit, leukocytes, differential count, total neutrophils and lymphocytes, platelets, reticulocytes and erythrocyte sedimentation rate were utilized for this analysis. These tests were chosen for several reasons. They can be done in most hospitals and laboratories; they require little blood and more data are made available than in other types of study. The method of analysis by assignment of profile values is shown in Table VI. After determining the normal range of each test, values of 1 to 4 were assigned to increasing deviations from normal. Thus each test could be summed when performed systematically to give both integral and cumulative scores. Table VII lists the recommended diagnostic procedures and the optimal times at which these studies can be done. The studies shown as *Type A* are particularly useful for early diagnosis and prognosis; *Type B* studies are of more help in confirming earlier injury estimates and in recognizing and managing complications; *Type C* studies are of possible but not yet verified value for future use in the previous categories. Many additional studies may be desirable and necessary but these suggested routines will assure a thorough and well organized plan of action in handling rather complex problems.

The peripheral blood count remains the most valuable test available for indicating radiation injury and following its course. Using the profile scoring system it became possible to separate Group I and II patients from the sicker patients in forty-eight hours or less (Fig. 3). Group V was distinguishable from the beginning. By the sixth day Group I was distinct from Group II, and Group III from Group IV. There is, however, significant overlap in the first few days.

The total lymphocyte count enabled separation into Groups II, III, and IV rather promptly and within forty-eight hours. The neutrophil and leukocyte scores helped in group differentiation by the third day. The platelet score showed a distinction between Groups III and IV by the sixth day and after the third week Groups II and III were sharply separated from Group I. An indication of the alterations in the total blood picture for 5 men exposed to 236–365 rad of mixed neutron-gamma radiation in the Oak Ridge accident is shown in Figure 4. The marked fall in platelets and total white blood cell count is evident from the fifth to the fortieth days.

TABLE VI

PROFILE VALUES ASSIGNED FOR VARIOUS RANGES OF ABNORMALITY
Hematology—Peripheral Counts

Test	Units	Normal*	Profile Value							
			1	2	3	4	1	2	3	4
			(for increase above normal)				(for decrease below normal)			
Hemoglobin	gm. per cent	M–15.8	18	19	20	21	14	12	10	8
		F–13.9	16	17	18	19	11.5	10	8.5	7
Erythrocytes	Mill./mm.^{3}	M– 5.4	6.0	7.0	8.0	9.0	4.5	3.5	2.5	1.5
		F– 4.8	5.5	6.5	7.5	8.5	4.0	3.0	2.0	1.0
Hematocrit	Volume per cent	M–47	54	56	58	60	40	35	30	25
		F–42	47	49	51	53	37	32	27	22
Leukocytes	1,000/mm.^{3}	7.4	12	18	24	30	4.0	3.0	2.0	1.0
Neutrophils	1,000/mm.^{3}	4.4	7.7	14	21	28.0	1.8	1.3	0.9	0.5
Lymphocytes	1,000/mm.^{3}	2.5	4.8	7.0	10	12.0	1.0	0.75	0.5	0.3
Platelets	1,000/mm.^{3}									
Rees-Ecker		405	545	700	850	1,000	273	200	100	30
Brecher-Cronkite		257	440	600	750	900	140	100	50	30
Fonio		234	350	500	650	800	130	100	50	30
Dameshek		716	900	1,000	1,500	2,000	500	350	100	30
Reticulocytes	per cent red blood cells	1.5	4	8	15	25	.5	0		
Erythrocyte Sedimentation Rate	mm./hr.	M– 5	10	20	30	40				
		F–10	20	30	40	50				

* Expressed as "universal mean" value. Taken from Standard Values in Blood: Being the First Fascicle of a Handbook of Biological Data. E. C. Albritton, Editor. W. B. Saunders Company, Philadelphia, 1952.

The blood picture did not reveal any clear indication of the onset of complications. The erythrocyte sedimentation test was elevated in the early stages of infection but remained elevated long after the infection abated. The coagulation time was prolonged in 3 of the Los Alamos patients. In the 1 who died on the ninth day there was progressive prolongation. An increase in clotting time was noted frequently in the Yugoslavian patients. Other tests of the coagulation mechanism were occasionally used and showed abnormalities of plasma clotting, perhaps related in part to the thrombocytopenia.

Blood electrolyte measurements were of particular value in cases of prolonged diarrhea and vomiting. Nitrogen retention was found in patients with oliguria.

Urinary output was found to be decreased to oliguric levels in almost all patients in Group III or above. Quantitative determinations of urinary aminoacids showed increases in a variety of these within twelve hours but there was no correlation with dose. In the Group II Oak Ridge patients there was increased excretion of beta-aminoisobutyric acid, which was maximal during the first few days, returning to normal values by the tenth day. The excretion levels seemed proportional to dose.

Tests for determination of radioactivity in exposed individuals are required in two types of accidents. In the situation where neutrons are involved, radioactive Na^{24} is produced from stable Na^{23} by a neutron, gamma reaction. The level of Na^{24} in blood and urine can be used as an index of the neutron dose received. A satisfactory estimate of Na^{24} in blood can be made with only 5–10 ml. of whole blood using a standard 2 inch well-type scintillation counter. The second situation in which radioassay procedures are of value is following contamination with radionuclides. In this type

TABLE VII

RECOMMENDED DIAGNOSTIC PROCEDURES FOR CLINICAL MANAGEMENT OF RADIATION INJURY*

Group	I-II-III-IV			I	II			III		IV	V
Postexposure Day	1	2	3	4–∞	4–17	18–48	49–∞	4–48	49–∞	4–∞	1–∞
Type A Studies											
History											
Symptoms (onset and duration)	D	D	D	S	S	D	S	D	S	D	D
Signs	D	D	D	S	S	D	S	D	S	D	D
Past medical	D										
Physical examination											
General	D					21d	S90d	15d and 30	S90d	6d	D
Body weight	D			S	S	D	S	D	S	D	D
Urinary output	D	D	D		S	D		D		D	6h
Laboratory Tests											
Hematology											
Hematocrit	D	D	D	S	S	D	S	S	S	D	6h
Leukocytes	D	D	D	S	S	D	S	D	S	D	6h
Differential count	D	D	D	S	S	D	S	D	S	D	6h
Calculation of total neutrophils and lymphocytes	D	D	D	S	S	D	S	D	S	D	6h
Platelets	D	D	D	S	S	D	S	S	S	D	6h
Bone marrow aspiration		D		30d	14d	14d	6m	14d	6m	7d	D
Radioassay											
Blood Na^{24}	D	D									
Whole body counting	D	D									
Type B Studies											
Hematology											
Sedimentation rate	D	D	D	S	S	D	S	D	S	D	6h
Reticulocytes	D	D	D	S	S	D	S	S	S	D	6h
Bleeding and clotting times	D					S		S	75dS	3d	6h
Blood Chemistry											
Nonprotein nitrogen	D	prn	prn					prn		S	6h
Sodium	D	prn	prn					prn		prn	D
Chloride	D	prn	prn					prn		prn	D
Potassium	D	prn	prn					prn		prn	D
pH or CO_2	D	prn	prn					prn		prn	D
Urine											
Routine analysis	D	D	D		S	D	S	D	S	D	6h
Stool											
Occult blood	D					D		S12d		D	D
Ophthalmology											
Slit lamp			D	S6m			S6m		S6m		
Type C Studies											
Biochemistry											
Serum bilirubin	D	D	D		S	S		S		D	6h
Urine BAIBA	D			30d	S	D		D		D	D

* D = Daily during time indicated by column heading.
S = Those standard performance times (*i.e.*, day 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 40, 44, 48, 60, 75, 90, 105, and 120, 6 mo., 1 yr. and annually) which occur within period indicated by column heading.
prn = as necessitated by clinical course.
h = hour. d = day. m = month.

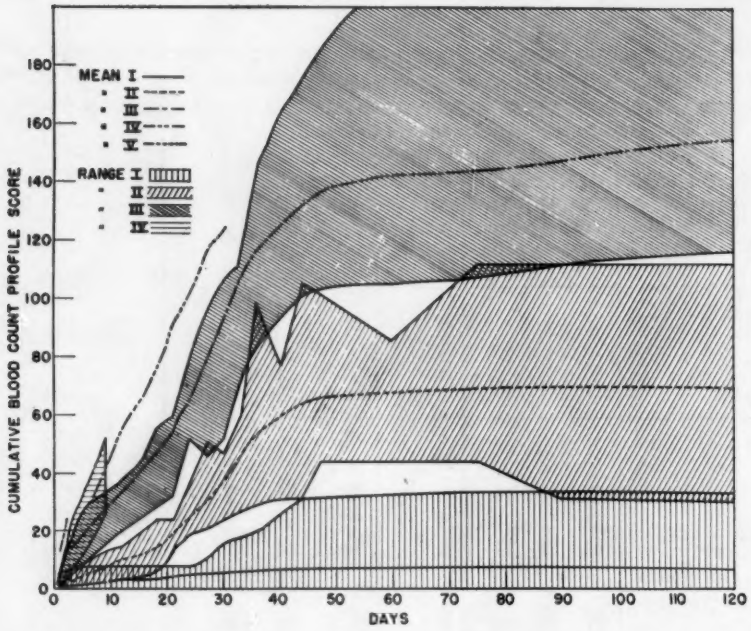

FIG. 3. Graph of means of cumulative blood count profile scores of injury groups in respect to time for 31 patients exposed to external radiation.[17] (Reproduced by permission from the *Journal of Occupational Medicine*.)

of accident, wipes of skin, nose, and ears should be made. All urine and stool samples should be saved at least for twenty-four to forty-eight hours, until the accident has been suitably analyzed.

Another method of determining radioactivity of an exposed individual is by using the whole body counter. These instruments are extremely sensitive and accurate gamma detectors which can provide estimates of very small amounts of radioactivity in the body. They are essentially of two types. One type consists of a large tank or chamber of a liquid scintillator with many phototubes feeding into a recording system. This type has somewhat greater sensitivity for very low levels of activity and will provide a measure of total activity in the body. It is not capable of differentiating several radionuclides which might be present. The second type of whole body counter consists of a very large crystal of 4–9 inch diameter in a heavily shielded room of 5–10 inches of iron. The subject sits or lies in such a position that the radiation from the entire body or various parts is counted. The signal from the photomultiplier is fed to a multichannel pulse height analyzer and various gamma emitting radionuclides can be distinguished. The total sensitivity of such a counter may be somewhat less than that of the liquid scintillator. These installations are costly and only nine are presently available in the United States. In a contamination type of accident, patients should not be placed in a total body counter until all possible surface contamination has been removed. Otherwise the counter may be so thoroughly contaminated that it will be useless for a long time. A special use of the iron shielded room is for penetrating wounds involving plutonium. By using special thin crystals in the low background area, the 17 kev. gamma ray of Pu^{239} can be detected as an important guide in surgical excision.

THERAPY

The treatment of the acute radiation syndrome remains supportive with specific therapy utilized for various complications.

In general, if there is a question of serious

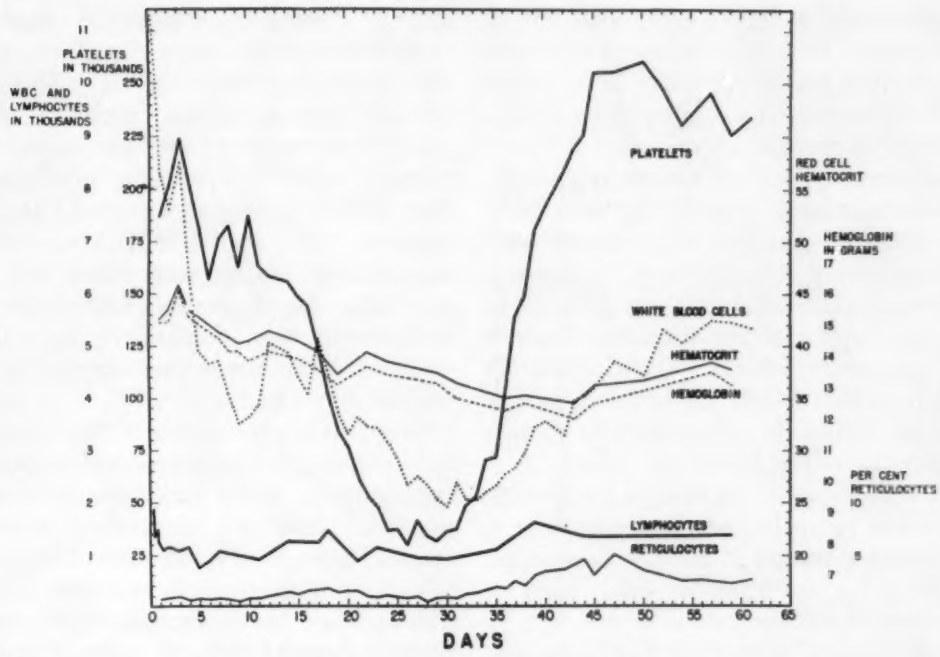

Fig. 4. Average values of blood elements of 5 individuals exposed to estimated doses of 236 to 365 rad at the Oak Ridge criticality accident of June 16, 1958.[2]

overexposure in any type of radiation accident, hospitalization is desirable. Within two to three days those patients with less than 100 rad can be identified and followed either as outpatients or in convalescent wards. Patients whose doses are above 100–150 rad should remain under very close observation in the hospital.

In the Group II patients (200–400 rad) antiemetic agents, tranquilizers and reassurance will usually suffice during the prodromal stage. Whenever possible the patients should be isolated from each other to minimize group generated apprehensions. During the latent period, emphasis on careful personal hygiene and aseptic isolation precautions may help to minimize the onset of complications of infection during the period of manifest illness. When this latter stage is reached, a conservative attitude of watchful waiting with vigorous and definitive therapy for complications seems preferable to shotgun treatment for all possible complications. Antibiotics, blood and platelet transfusions should be immediately available. This conservative approach was particularly effective in the management of the Oak Ridge patients.[2] Many of these patients exhibit marked fatigue and weakness for several months. No specific therapy is available for these complaints at present.

The Group III patients (400–600 rad) present the most stimulating challenge for well planned therapy. There will be major complications of serious bone marrow damage, gastrointestinal injury and secondary renal and cardiovascular problems. Bed rest and good nursing care are essential as soon as the diagnosis is suspected. Antiemetics, sedation and parenteral fluids for maintenance of electrolytes, water and caloric needs should be given as needed, particularly for gastrointestinal symptoms. Close watch of blood electrolytes is important. To protect against infections, isolation and aseptic techniques for these patients are desirable. Prophylactic antibiotics have been recommended and used; their real helpfulness has not been clearly demonstrated. Some evidence suggests that the prophylactic use has blunted their later effectiveness. It is probable that the use of

parenteral antibiotics in high doses begun at the earliest indication of overt or occult infection is a preferable plan. The beginning infection may be suggested by symptoms such as fever or elevation of erythrocyte sedimentation rate. Depending on the time after exposure, leukocytosis may be of little value. If possible, appropriate bacterial sensitivity studies should be done.

Hemorrhagic phenomena are difficult to treat, although platelet transfusions may show temporary benefit. Anemia will respond to whole blood transfusion, which should be used only when there is significant decrease of red blood cell volume.

A new therapeutic technique for pancytopenia has recently been attempted in 5 Yugoslavian patients in Paris.[12] Bone marrow transplantation using cells from a homologous donor matched in sex and in major and minor subgroup was done approximately one month after exposure. Previously it had been thought necessary to carry out such a technique within a few days after exposure. This experience indicates that one can observe the clinical course prior to such therapy. It removes the urgency of proceeding with a difficult form of therapy when there are few clinical and only fragmentary dosimetric data immediately after the exposure.

In the treated patients there was a prompt rise to a peak of granulocytes, platelets and reticulocytes before similar improvement was found in a lower dose patient who was recovering spontaneously. Red blood cell agglutination indicated a phase of increase in the number of donor cells when transfused cells would have been decreasing. Further experience may show that bone marrow transfusion serves as a temporary support during the time when the patient's marrow function is inadequate. The over-all value of the procedure has not been fully determined. It should be reserved as a desperate measure in the face of overwhelming odds in severely irradiated patients pending further studies.

Group IV patients (600–1,400 rad) showed a more rapid downhill course than Group III, one dying on the ninth day and the other on the thirtieth day. There were serious gastrointestinal problems. Tubal gastric decompression, parenteral fluid therapy with maintenance of electrolyte and caloric needs, antiemetics, antihypotensives, antibiotics and bone marrow transfusion are suggested. Renal and cardiovascular complications occurred in the 2 patients of this group. Dialysis with an artificial kidney was not helpful in the 1 patient so treated.

Only 1 Group V patient has been carefully studied.[16] The massive dose received (12,000 rem, 9,200 rad) produced a fulminating downhill course of thirty-six hours. Therapy directed toward mitigation of shock and gastrointestinal complications was utilized. No recommendations can be given at present for such a situation.

Many problems also arise in the handling of patients contaminated with radionuclides. In the case of the Marshall Islanders,[3] the dose received from external radiation and skin contamination was sufficient to produce changes of the acute radiation syndrome. Careful cleansing of the skin is important. Finkel and Hathaway[4] present an excellent discussion of decontamination with particular reference to surgical indications and techniques.

CONCLUSIONS

There have been some interesting developments in efforts to mobilize certain radionuclides which have become fixed in the body. Studies over the past several years[14] have shown that zirconium citrate or maleate as colloidal ion exchange carriers and calcium disodium ethylene diamine tetra-acetic acid (EDTA), a chelating agent, increased excretion of plutonium and certain other radionuclides by factors of 6–10. Recently a new chelating agent, trisodium calcium diethylene-triamine pentacetic acid (DTPA), has been carefully studied both in animals and humans. Norwood[13] has reported on the effects of

DTPA in 6 patients who had varying plutonium body burdens from inhalation or wounds. He found urinary excretion increased by factors of 45–120 and fecal excretion to be increased by factors of 2–8.

The effectiveness of DTPA is shown in Figure 5. This graph depicts the plutonium excretion pattern of a forty-three year old man who had inhaled Pu^{239} accidentally 2.5 years before therapy. Prior to therapy the average twenty-four hour output of Pu^{239} expressed as disintegrations per minute was 7.25. After treatment with DTPA in doses of 1 gm. intravenously three times per week, the excretion level rose to 742 d/min. The ratio of Pu^{239} output after treatment level/before treatment level was 102. Treatment with EDTA in this same patient following the exposure increased urinary output by a factor of 10. Since the average increase in the after treatment level/before treatment level with repeated courses is about 40 and since his body burden of Pu^{239} is several times the maximal permissible limit, he is maintained on a dose of 1 gm. of DTPA twice weekly for three weeks followed by a rest period of three weeks. This course should result in clearing the body to a permissible limit (0.6 μg.) in less than six months. Of particular interest is the observation that the effect of DTPA persists for several days after injection, this finding being noted in the 6 patients so treated. In contrast, using EDTA in rats, 95–98 per cent of the injected dose is excreted in a matter of hours. For accidental exposure an initial single dose of 1 gm. should be given followed by successive 1 gm. doses two or three times weekly. For extended courses a three week period of treatment should be alternated with a three week period of rest. If the plutonium deposition is large, the dose should be doubled or tripled initially.

These chelating agents can produce toxic nephrosis. A number of deaths in humans due to acute renal failure have been reported following EDTA therapy of individuals with renal disease. The renal status of the patient must be evaluated prior to DTPA therapy and must be followed carefully during and after treatment. These drugs should not be used in the presence of renal disease.

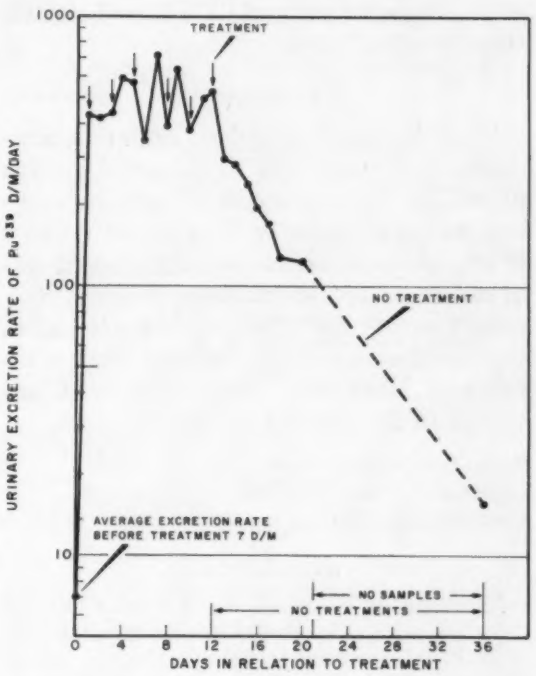

Fig. 5. Curve showing twenty-four hour excretion of Pu^{239} before, during and after administration of DTPA in doses of 1 gm. three times per week (Monday, Wednesday and Friday).[13] Treatment times are shown by arrows. Therapy was started 2.5 years after deposition of Pu^{239}. (By courtesy of Dr. W. D. Norwood.)

At present there are few human data concerning the efficacy of DTPA in the treatment of deposition of other radionuclides. Animal studies have shown DTPA to be more effective than other chelating agents for the removal of mixed fission products, uranium, thorium, yttrium, lanthanum and cerium. It has not been effective in increasing the elimination of Sr^{85} or lead. Kroll *et al.*[11] studied the elimination of tracer doses of radioyttrium and radiolanthanum following chelation with DTPA or with cyclohexane 1, 2 transdiamine tetra-acetic acid (CDTA). Removal of these radionuclides in humans was more efficient with DTPA

and CDTA than when EDTA was used as the chelating agent.

SUMMARY

The likelihood of serious radiation accidents is increased due to the rapid growth of nuclear technology in science, industry and national defense. This paper reviews briefly the possible causes of various types of radiation accidents. Suitable emergency programs are described. The acute radiation syndrome is discussed both from clinical and laboratory aspects. Recent advances in therapy are described.

Radio-Isotope Laboratory
Cincinnati General Hospital
Cincinnati 29, Ohio

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VOL. 84, NO. 4

DETERMINATION OF HALF-VALUE LAYER

By E. DALE TROUT, B.S., D.Sc., JOHN P. KELLEY, B.S., *and* ARTHUR C. LUCAS, B.S.
MILWAUKEE, WISCONSIN

DURING the course of evaluating a new roentgen-ray therapy unit, it was noted that, at the same voltage with the same treatment filters used at the same position in the beam, the half-value layers measured were different by as much as 10 per cent at the maximum voltage and filter used. In making the half-value layer determinations, both treatment filters and added filters were at the same position in the beam. The measured half-value layer was always associated with the beam defining system; one employed cones and the other a visual localizer. The only difference in the two systems was that, when cones were used to define the beam, the defining diaphragm was 12 cm. from the focal spot, whereas, when the visual localizer was used, the defining diaphragm was 25 cm. from the focal spot. In both cases the field at the measuring chamber was 10×10 cm. The location of the various elements is shown in Figure 1. Further examination confirmed the natural assumption that the half-value layer would also vary with the position of the filter in the beam.

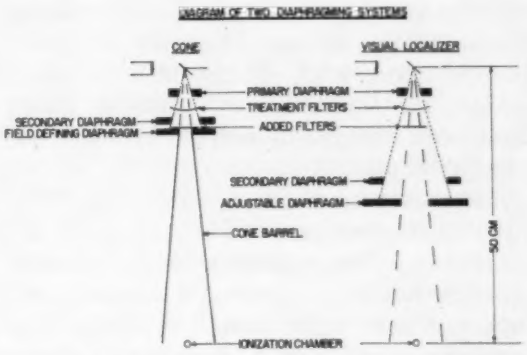

FIG. 1. Diagram of two diaphragming systems.

A survey of the literature available to us led to the conclusion that, although most radiologists and radiation physicists were aware of the fact that geometry had a bearing on determinations of this type, most of the knowledge evolved around the two terms, "poor geometry" and "good geometry." It was difficult to arrive at any definition as to just what was represented in the two terms and just as difficult to arrive at any conclusion as to the effect of "good" and "poor" geometry on the resulting measurement. Most of the references available contained a meager amount of data, this lack of data probably being due to the limitations inherent in the equipment that had been used. In general, the recommendation is made that the fields should be small without stating whether this is a small field at the filter or at the chamber, and that long distances should be used. Naturally, the question arises as to what is a small field and a long distance. In the English literature, only two references were found in which specific recommendations were made having to do with methods under which half-value layer measurements may be made. These were a paper by R. F. Farr[2] in *Acta Radiologica*, February, 1955, and H. E. Johns'[5] book, "The Physics of Radiation Therapy." In view of this, it was thought worth-while to explore all the variables involved, making full use of the capabilities of the equipment that had become available in our laboratory. In so doing, we wish to take cognizance of similar work on specific parts of the problem undertaken and reported by other investigators. Our only contribution may consist in expanding general knowledge and bringing it into a single presentation.

The roentgen-ray source under investigation and that used for the study reported here consisted of a resonant transformer operating at a nominal frequency of 1,200 cycles and a grounded anode, beryllium window tube, and capable of operation at from 100 to 300 kv. peak at tube currents up to 20 ma. An electronic power source supplied the 1,200-cycle input to the high-

voltage transformer, and excellent stabilization of both kilovoltage and tube current was had by making use of feedback loops operating on kilovoltage and tube current signals developed in the high-voltage system. Some of the information developed in this study could not have been obtained with equipment of previous design, for significant information would have been lost due to lack of short time reproducibility.

The reproducibility of kilovoltage and tube current was further enhanced by monitoring these signals with d-c potentiometers having 0.1 per cent accuracy and 0.05 per cent reproducibility. Dose rates were measured with a Townsend balance system using a 0.1 per cent potentiometer as the readout element and a D.C. amplifier as a null detector. The greater part of the data presented was taken using a 25 r Victoreen chamber. Some of the low energy data were taken using a 250 r Victoreen end-window, low energy chamber. Some of the scatter measurements necessitated the use of a small, thin wall chamber designed specifically for such measurements.

All chambers used were calibrated against a Victoreen r meter and associated chambers calibrated at the National Bureau of Standards. Particular attention was paid to wavelength dependence and saturation.

Since differences in the determination of the half-value layer were thought to be related to radiation scattered from the filter, the variables would seem to be the irradiated filter area, focal-filter distance, and focal-chamber distance. Accordingly, a series of experiments was devised to show the effect of each on the resulting half-value layer determination.

METHOD AND RESULTS

A set of 7 mm. thick lead diaphragms was constructed having round apertures 1.5 to 10.0 cm. in diameter. By making use of an optical bench, the focal-diaphragm distance and the focal-chamber distance could be varied from a minimum of 10 cm.

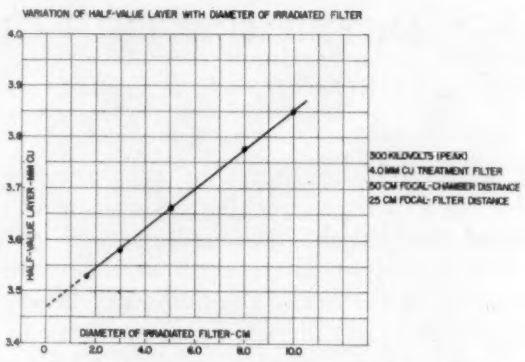
VARIATION OF HALF-VALUE LAYER WITH DIAMETER OF IRRADIATED FILTER
HALF-VALUE LAYER-MM CU
DIAMETER OF IRRADIATED FILTER-CM
300 KILOVOLTS (PEAK)
4.0 MM CU TREATMENT FILTER
50 CM FOCAL-CHAMBER DISTANCE
25 CM FOCAL-FILTER DISTANCE

Fig. 2. Variation of half-value layer with diameter of irradiated filter.

to a maximum of 200 cm. from the focal spot. All filters were placed at the diaphragm position. Care was taken to irradiate the diaphragm with a beam larger than the aperture but smaller than the diaphragm.

At 300 kv. peak, with a 4.0 mm. copper treatment filter, a focal-chamber distance of 50 cm., and the filter-diaphragm assembly midway between the focal spot and the chamber, the half-value layer was determined for each of the apertures. In Figure 2 the resulting half-value layers are shown plotted against the diameter of the aperture.

The effect of focal-filter distance on the measured half-value layer was investigated by moving the filter-diaphragm combination along the optical bench while maintaining a constant focal-chamber distance. In maintaining a field of constant diameter at the filter, the field at the chamber often became very large. In such cases, additional shielding was used around the preamplifier and portions of the stem to avoid the possibility of leakage. The half-value layers determined for a 10 cm. diameter aperture, focal-chamber distance of 100 cm., 300 kv. peak, and 4.0 mm. copper treatment filter are shown in Figure 3. A broad minimum consistently appeared with the filter-diaphragm combination midway between the source and the chamber. Within the limits of experimental error, the curve was always symmetric

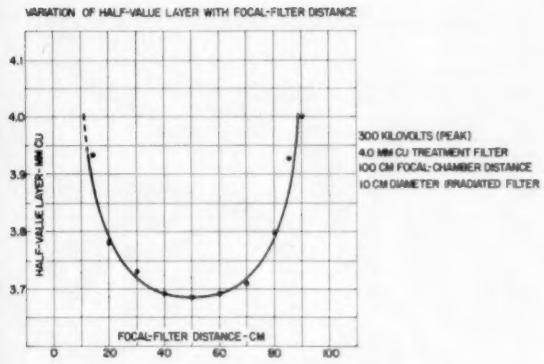
VARIATION OF HALF-VALUE LAYER WITH FOCAL-FILTER DISTANCE
HALF-VALUE LAYER-MM CU
FOCAL-FILTER DISTANCE-CM
300 KILOVOLTS (PEAK)
4.0 MM CU TREATMENT FILTER
100 CM FOCAL-CHAMBER DISTANCE
10 CM DIAMETER IRRADIATED FILTER

Fig. 3. Variation of half-value layer with focal-filter distance.

about this mid-point. This is consistent with the work of Seemann[7] in his consideration of the scattering of light from an optical filter and secondary radiation from filters in a roentgen-ray beam.

Using a focal-filter distance equal to one-half the focal-chamber distance, the half-value layer was measured for focal-chamber distances from 30 to 200 cm. using a 10 cm. aperture. The resulting half-value layers are plotted against focal-chamber distance in Figure 4. It will be seen that the half-value layer decreases as the focal-chamber distance is increased and levels off at the longer distances, This would seem to justify the long distance prescribed as part of the definition of "good geometry."

It seems apparent that there is some need for a common denominator to which all half-value layer measurements could be reduced. In the past, there has been the problem of comparing published data on such things as backscatter and depth dose for half-value layers determined under different or unreported conditions. These are only a few of the radiation effects related to half-value layer, and one less variable would be involved if all stated half-value layers were reduced to some common denominator which would relate them to some accepted geometry.

Fortunately, in the past, equipment design was such as to place filters approximately midway between the focal spot and the end of the treatment cone, which was usually the chamber position. The result was fairly good agreement for all available equipment. Recent apparatus design has altered this condition, in some cases, by placing the treatment filter closer to the focal spot and by putting the diaphragm in some previously inaccessible position. As a result, there is a wider spread in the geometry which may be used. There is another complicating factor in that there is a tendency to combine voltage and filter selection to provide a control selector position designated by half-value layer. All these elements combine to make desirable some system by which it is possible to arrive at a half-value layer expressing beam quality regardless of the geometry used in making the measurement. Farr[2] uses the term "unique" to describe this half-value layer. From the experimental data presented herewith, it is possible to make some suggestions as to a method of arriving at a unique half-value layer. Possible solutions might be to: (1) confine the measuring geometry to one that would reduce the scattered radiation from the filter to some negligible level; (2) use an extrapolation technique that would result in a unique half-value layer; and (3) derive a system of corrections which, when applied to measurements taken under known conditions, would result in a unique half-value layer.

The first solution would be applicable to a limited number of practical cases in which

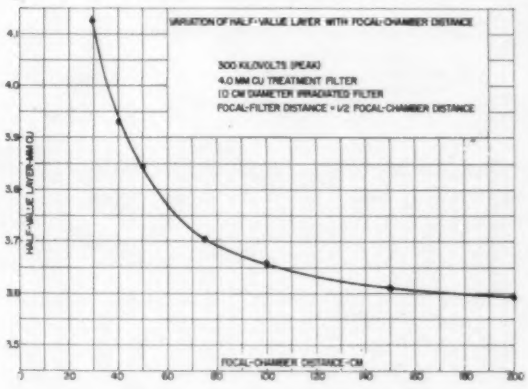
VARIATION OF HALF-VALUE LAYER WITH FOCAL-CHAMBER DISTANCE
300 KILOVOLTS (PEAK)
4.0 MM CU TREATMENT FILTER
10 CM DIAMETER IRRADIATED FILTER
FOCAL-FILTER DISTANCE = 1/2 FOCAL-CHAMBER DISTANCE
HALF-VALUE LAYER-MM CU
FOCAL-CHAMBER DISTANCE-CM

Fig. 4. Variation of half-value layer with focal-chamber distance.

the beam could be suitably restricted and the output of the source is sufficient to allow data to be taken at great distances. In general, it is more difficult to determine the half-value layer as accurately at long distances as at short distances due to the fact that the smaller ionization currents involved and the necessarily critical alignment of source, diaphragm, and chamber increases the relative uncertainty in each dose rate determination. It is possible to partially offset this uncertainty by making several determinations and taking an average. A 1 cm. aperture with filters and aperture midway between focal spot and measuring chamber and a focal-chamber distance of 100 cm. would reduce the error due to scatter to less than 1 per cent at 300 kv. peak with a treatment filter of 4.0 mm. copper, assuming that the field so provided would cover the measuring chamber.

In considering the extrapolation technique, one solution would be an extrapolation of the half-value layer to infinite distance using a constant field size and a focal-filter distance one-half the focal-chamber distance. Figure 5 shows a plot of measured half-value layer against the reciprocal of focal-chamber distance. Data are shown for 5 and 10 cm. diameter fields at the filter. This extrapolation is not attractive and believed to be of limited accuracy since the precision with which half-value layer measurements can be made decreases with distance.

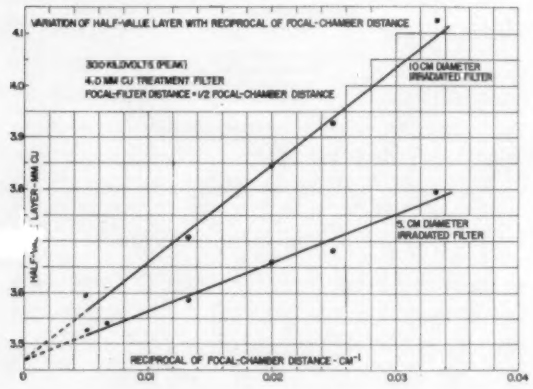

Fig. 5. Variation of half-value layer with reciprocal of focal-chamber distance.

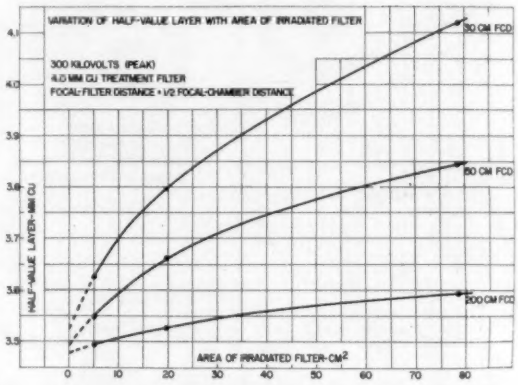

Fig. 6. Variation of half-value layer with area of irradiated filter.

An extrapolation to zero field is more attractive since distance is often limited by room size and commercially available apparatus usually have variable field definers or interchangeable cones making it easy to vary field size. One would expect a half-value layer measured with negligible scattering area to be independent of other geometric factors. This is to say, an extrapolation of data to zero area or zero diameter ought to yield a unique measure of beam quality. Plots of half-value layer against area, shown in Figure 6, are very difficult to extrapolate to a unique intercept because of the changing slope of the curve. In our investigations, plots of half-value layer against diameter, as shown in Figure 7, yield a unique intercept for all combinations of focal-filter distance and focal-chamber distance.

Since effects of this kind are normally considered to be area dependent and the form of the extrapolation will alter the magnitude of the intercept considerably, a somewhat more rigorous test of the linearity with diameter would be desirable. Accordingly, a set of 10 mm. thick lead disks and apertures was made. The diameter of each disk was 2 cm. less than that of a corresponding lead aperture. By supporting the lead disks at the center of the apertures and placing an ionization chamber on the axis of the system, scatter from an annular segment of filter could be studied by adding

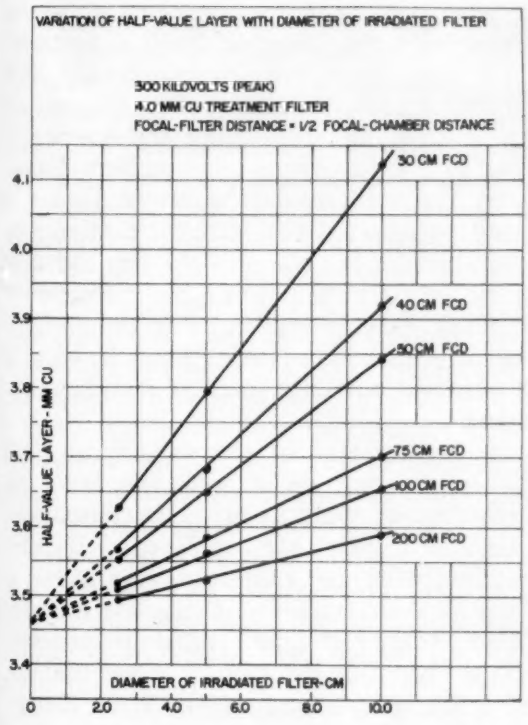
VARIATION OF HALF-VALUE LAYER WITH DIAMETER OF IRRADIATED FILTER
300 KILOVOLTS (PEAK)
4.0 MM CU TREATMENT FILTER
FOCAL-FILTER DISTANCE = 1/2 FOCAL-CHAMBER DISTANCE
30 CM FCD
40 CM FCD
50 CM FCD
75 CM FCD
100 CM FCD
200 CM FCD
HALF-VALUE LAYER - MM CU
DIAMETER OF IRRADIATED FILTER-CM

FIG. 7. Variation of half-value layer with diameter of irradiated filter.

filters at the aperture. Since the size and wall thickness of the 25 r Victoreen chamber were considered unsuitable for these measurements, a small, thin wall chamber was constructed. Its volume was about 0.09 cc. and its wall thickness was 9.5 mg./cm.^{2}. In comparison, the 25 r Victoreen thimble chamber has a nominal volume of 1.83 cc. and a wall thickness of 67 mg./cm.^{2}. Wavelength dependence of the thin wall chamber was negligible between half-value layers 3.0 mm. aluminum at 100 kv. peak and 4.0 mm. copper at 300 kv. peak, and the correction rose smoothly to 1.20 at 20 kv. peak with 2 mm. beryllium inherent filtration. Data which follow were taken with this small chamber.

Figure 8 shows the scatter from annular segments of filter 1 cm. wide having average diameters of 4.0, 6.5, and 9.0 cm. One observes first that, within the range of filtration encompassed by the measurement of the half-value layer, the amount of radiation scattered to the ionization chamber does not vary as much as the primary beam

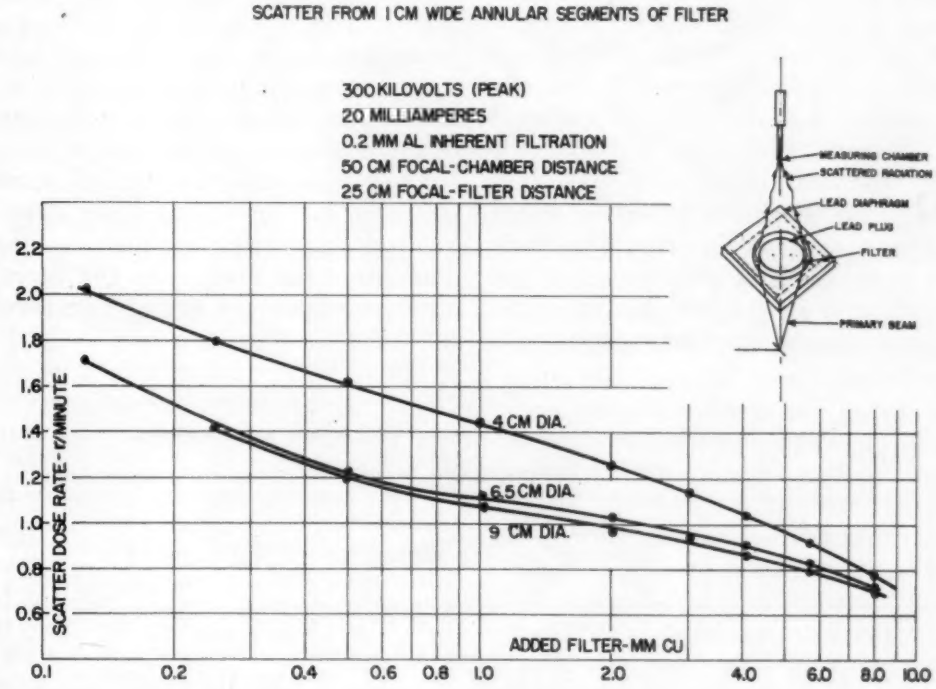

FIG. 8. Scatter from 1 cm. wide annular segments of filter.

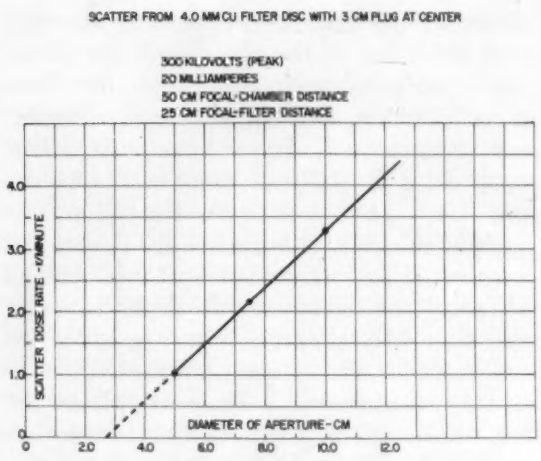

Fig. 9. Scatter from 4.0 mm. copper filter disk with 3 cm. plug at center.

dose rate. For example, at 4.0 mm. copper, the addition of a half-value layer reduces the primary beam dose rate 50 per cent while the scatter is reduced only 20 per cent. This accounts for the fact that the measurement of the half-value layer is dependent upon geometry, for, if the scattered dose rate were to decrease by a factor of 2 upon the addition of a filter equal in thickness to the half-value layer, the measurement of the half-value layer would not be dependent upon geometry. One observes, further, that the radiation scattered from a segment of filter 4 cm. in diameter is not very different in amount from that scattered from segments equal in width but of greater average diameter. This lends support to the previous conclusion that the half-value layer is proportional to diameter, since a summation of the contributions from succeeding annular segments would be linear with the diameter. Such a summation was performed experimentally by placing a 3 cm. diameter disk on the axis of the system and measuring the scattered dose rate for apertures of increasing diameter. The resulting data shown in Figure 9 were found to be linear with the diameter of the aperture but the straight line did not quite intersect the axis at 3, the diameter of the disk. This is consistent with the slightly higher scattered dose rate shown in Figure 8 obtained with the smallest annular segment.

A further test of the validity of the linear extrapolation of half-value layer to zero diameter may be made by comparing the half-value layer obtained by that method with the value obtained using a long focal-chamber distance and a narrow beam. Table 1 shows a comparison of half-value layers determined by extrapolation to zero diameter and narrow beam determinations made at several distances. The two half-value layer determinations listed for the linear extrapolation method were arrived at by extrapolations from four points. The half-value layer listed is the average of the two extrapolated values. The 2.5 cm. aperture used in the narrow beam determinations was chosen as the smallest diameter that would allow all of the chamber to receive radiation from all of the target area in the roentgen-ray tube. The half-value layer shown is the average of the determinations made and the percentage difference from the extrapolated value is shown.

Table I

COMPARISON OF EXTRAPOLATION METHOD TO NARROW BEAM METHOD

300 kv. peak—3.9 mm. copper filter

FCD (cm.)	FCD (cm.)	Aperture Diameter (cm.)	Determinations	HVL—mm. Cu	Difference (per cent)
100	50	Linear Extrapolation	2	3.342 ± .01	
100	50	2.5	3	3.382 ± .01	+1.2
200	100	2.5	11	3.365 ± .01	+ .69
400	200	2.5	7	3.354 ± .01	+ .35
Linear extrapolation to 1/D=0				3.345 ± .01	+ .09

The above experiments seem to provide, for practical purposes, sufficient proof of the validity of the extrapolation linear with the diameter. Tests to a greater accuracy of the validity of the extrapolation would require the use of a free air chamber and would be ultimately limited by machine stability and the current sensitivity of the measuring instrument.

The third possible solution for arriving at a unique half-value layer would be a method wherein a system of corrections is applied which results in a unique half-value layer from data taken under known geometric conditions. The practicality of such a method depends upon the availability of simple corrections.

The first correction, which we shall call K_1, needed in all cases, is one for the irradiated diameter of the measuring filter. Figures 10 and 11 show K_1, the fractional rise above the zero field half-value layer, for several combinations of voltage and filtration. These data were taken using a focal-chamber distance of 50 cm. and a focal-filter distance of 25 cm. The 50 cm. focal-chamber distance was chosen since it is a focal-chamber distance consistent with the voltage range under consideration. The 25 cm. focal-filter distance was chosen because the broad minimum in measured half-value layer occurs when the filter is midway between source and chamber.

A second correction, K_2, is needed for focal-filter distance other than half the

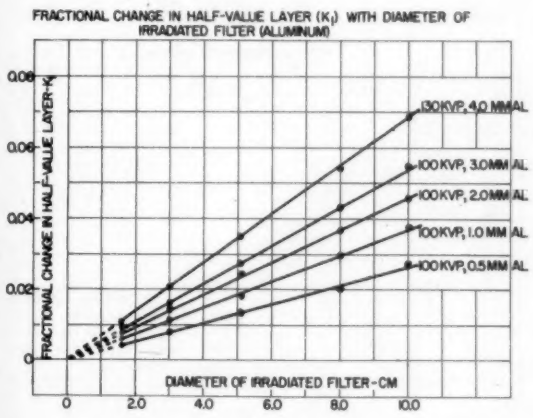

FIG. 10. Fractional change in half-value layer (K_1) with diameter of irradiated filter (aluminum).

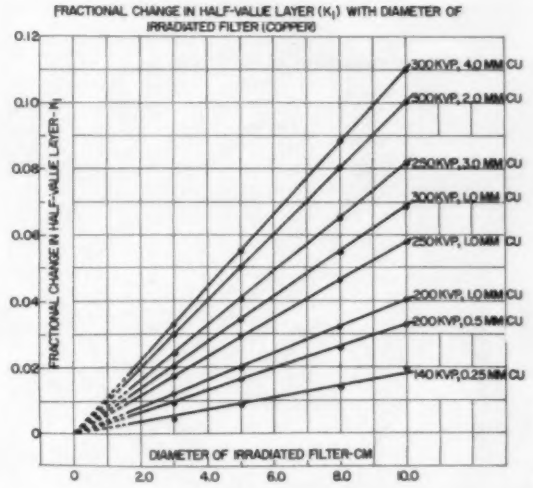

FIG. 11. Fractional change in half-value layer (K_1) with diameter of irradiated filter (copper).

focal-chamber distance. K_2 was computed from data shown in Figure 3 using the following formula:

$$K_2 = \frac{H - H_o}{H_m - H_o}$$

H = measured half-value layer at any point along a curve such as the one shown in Figure 3.

H_o = the zero field half-value layer taken from extrapolations such as that shown in Figure 2.

H_m = value of H at the point midway between the focal spot and the measuring chamber.

The physical significance of K_2 is shown diagrammatically in Figure 12.

This correction, shown in Figure 13, has been found to be almost entirely dependent upon the ratio of focal-filter distance to focal-chamber distance. There is some slight dependence upon the irradiated diameter of the measuring filter. The values shown represent a weighted mean with the greater weight being given to larger fields. Consideration of numerous data taken at half-value layers from 3.0 mm. aluminum to 4.0 mm. copper indicates that, within the limits of experimental error and conditions of usage, this correction could be considered to be independent of radiation quality.

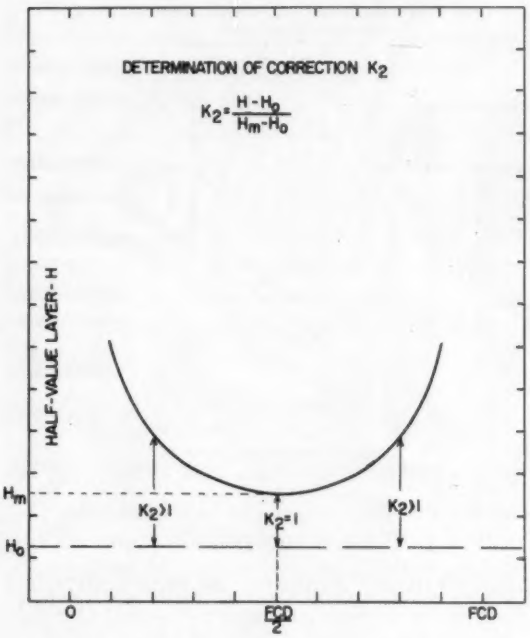

FIG. 12. Determination of K_2.

A third correction, K_3, shown diagrammatically in Figure 14, is needed for focal-chamber distance. K_3 was computed from the data in Figure 4 using the following formula:

$$K_3=\frac{H-H_o}{H_{50}-H_o}$$

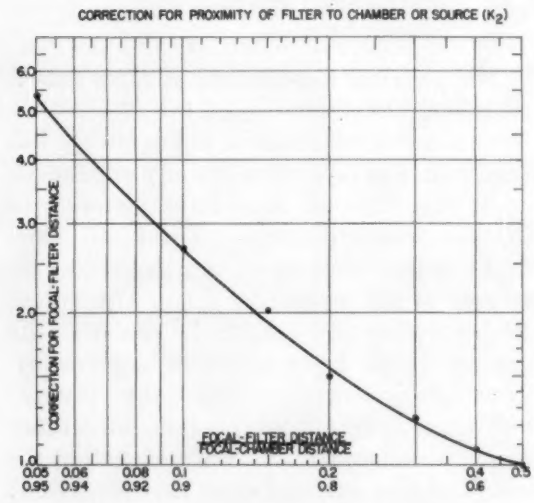

FIG. 13. Correction for proximity of filter to chamber or source (K_2).

H = measured half-value layer at any point along a curve such as the one shown in Figure 3.

H_o = the zero field half-value layer taken from extrapolations such as that shown in Figure 2.

H_{50} = half-value layer measured using a focal-chamber distance of 50 cm.

This correction has been found to be independent of kilovoltage, filtration, and irradiated diameter of measuring filter. Its value for focal-chamber distances from 15 to 100 cm. is shown in Figure 15.

The half-value layer for zero field is computed by applying corrections K_1, K_2, K_3 in the formula:

$$H_o=\frac{H}{1+K_1K_2K_3}$$

H = measured half-value layer.

H_o = zero field half-value layer.

K_1, K_2, K_3 = corrections described above.

Up to this point only round fields have been considered. Since many field defining devices provide square fields, it is of interest to know the diameter, d, of a round field which would result in the same half-value layer as that obtained with a square field of side, s. Since it has been shown that half-value layer is proportional to the diameter of a round field, a determination of average radius from the center of a square to its side yields the desired proportion.

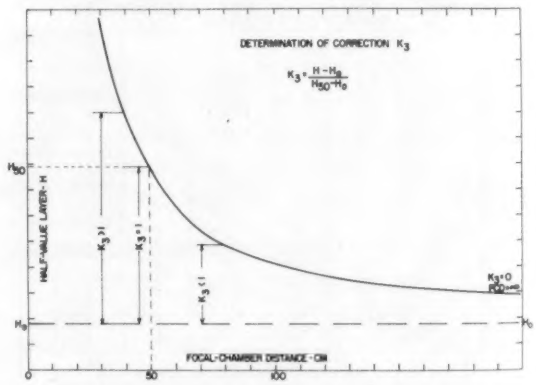

FIG. 14. Determination of K_3.

This integration has been performed and the ratio d/s was found to be 1.122. This ratio has been confirmed within the limits of experimental error both by measurement of the half-value layer and by measurement of the radiation scattered from square and circular fields in the development of correction K_1. When a square field is used, its side is simply multiplied by 1.122 and the resulting equivalent diameter is used to locate the appropriate value of K_1 in Figures 10 or 11.

An example of the application of the correction method would be: Measurement taken at the end of a 50 cm. open-end treatment cone providing a 10×10 cm. treatment field

300 kv. peak, 4.0 mm. copper treatment filter
Aperture at top of cone 4.4×4.4 cm., 12 cm. from source
Filters added at top of cone
Measured half-value layer, $H=3.75$ mm. copper
Equivalent circular field, $4.4\times1.122=4.93$ cm.
From Figure 11, $K_1=0.055$
FFD/FCD=0.24
From Figure 13, $K_2=1.38$
From Figure 15, $K_3=1.00$

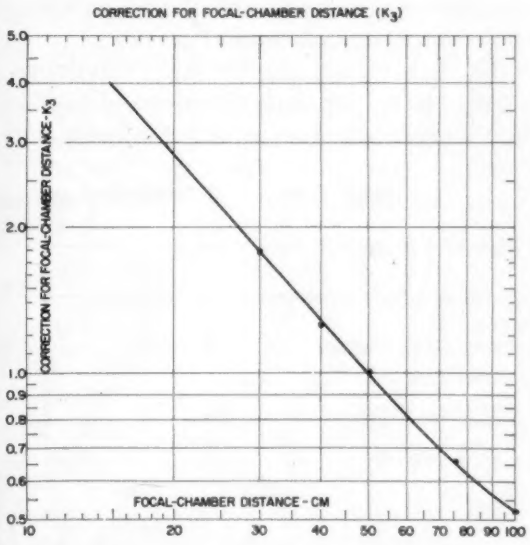

Fig. 15. Correction for focal-chamber distance (K_3).

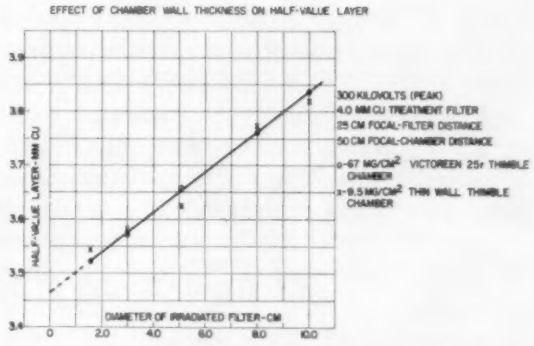

Fig. 16. Effect of chamber wall thickness on half-value layer.

$$H_o=\frac{3.75}{1+0.055\times1.38\times1.00}$$

$H_o=3.48$ mm. copper

It occurred to us that since the dependence of the half-value layer upon geometry is due to the presence of radiation scattered from filters, the data presented in Figures 10 and 11 for determining K_1 would not be valid for ionization chambers having more or less wall absorption than the one used to make these measurements. In order to demonstrate the possible effects of wall absorption on these measurements, data were taken using the small, thin wall chamber and the Victoreen 25 r chamber. Half-value layers so derived under identical conditions using each of the two chambers are shown in Figure 16. Data taken using the smaller chamber show greater statistical fluctuation because of the smaller ionization currents involved, but each set of data yields a straight line having a slope and intercept identical with the other. We have, therefore, concluded that, if the measuring chamber is free of wavelength dependence in the region encompassed by the primary spectrum, it will be free of wavelength dependence for the scattered spectrum of interest in making these measurements.

A comparison of half-value layer determinations made by the above three suggested techniques is shown in Table II. The "narrow beam" determination was made using a 100 cm. focal-chamber distance

TABLE II

COMPARISON OF HALF-VALUE LAYER DETERMINATIONS MADE BY THE THREE SUGGESTED TECHNIQUES

Kv. Peak	Treatment Filter	Measuring Technique		
		Narrow Beam	Extrapolation	Correction
		Half-Value Layer—mm.		
100	3.00 mm. Al	3.140 Al	3.121 Al	3.110 Al
140	0.25 mm. Cu	0.375 Cu	0.373 Cu	0.373 Cu
200	1.00 mm. Cu	1.285 Cu	1.275 Cu	1.280 Cu
250	3.00 mm. Cu	2.782 Cu	2.763 Cu	2.760 Cu
300	4.00 mm. Cu	3.498 Cu	3.465 Cu	3.480 Cu

with a 2.5 cm. diameter aperture and filters 50 cm. from the focal spot. The extrapolation was performed using data taken at a focal-chamber distance of 50 cm. and an aperture and filters 25 cm. from the focal spot. The correction technique was applied to data taken at the same distance using a 5 cm. diameter aperture. Agreement within 1 per cent was found in all cases.

The data in Table III indicate the lack of dependence of the extrapolation technique on the geometry of the diaphragming system. When treatment cones were used, the filters were added at the end of the cone and for the visual localizer the filters were added at the face of the localizer. It will be seen that the values are in good agreement for the two diaphragming systems when data are subjected to the extrapolation technique.

TABLE III

COMPARISON OF HALF-VALUE LAYER DETERMINATIONS USING EXTRAPOLATION TECHNIQUE WITH 50 CM. FSD CONES AND VISUAL LOCALIZER

Kv. Peak	Treatment Filter	Diaphragming System	
		50 cm. Cones*	Visual Localizer†
		Half-Value Layer—mm.	
100	3.00 mm. Al	3.119 Al	3.121 Al
140	0.25 mm. Cu	0.372 Cu	0.373 Cu
200	1.00 mm. Cu	1.275 Cu	1.279 Cu
250	3.00 mm. Cu	2.760 Cu	2.767 Cu
300	4.00 mm. Cu	3.462 Cu	3.465 Cu

* 50 cm. FSD treatment cones 5×5 cm. and 10×10 cm.; 50 cm. focal-added filter distance; 100 cm. focal-chamber distance.

† Visual localizer, 2.5×2.5 cm. and 5.0×5.0 cm. fields at filter; 25 cm. focal-added filter distance; 50 cm. focal-chamber distance.

Presently, the most difficult system in which to measure the half-value layer is that encountered in fluoroscopic equipment. There is a wide variation in the geometry encountered in the various types of tables and vertical fluoroscopes. It is usually quite difficult to determine the geometry involved without disassembling the equipment to determine the location of various filters, shutters, etc. In Table IV is shown the range of measured values of the half-value layer for several field sizes and two different positions of the filters using the arrangement shown in Figure 17.

The half-value layers for a typical fluoroscopic table were determined using each of the three techniques which we have sug-

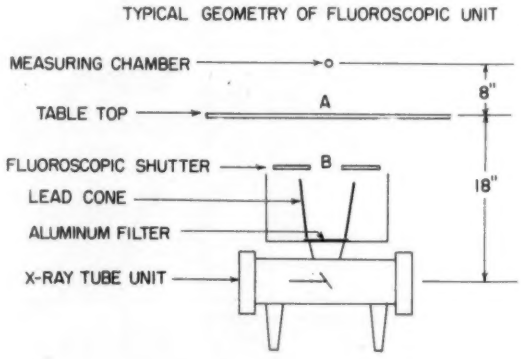

FIG. 17. Typical geometry of fluoroscopic unit.

TABLE IV

COMPARISON OF HALF-VALUE LAYER DETERMINATIONS: FLUOROSCOPIC GEOMETRY

100 kv. peak
2.5 mm. Al inherent filtration
26 inch focal-chamber distance
18 inch focal-table top distance

Added Filters at	Field at Table Top—cm.		
	2.5×2.5	5×5	10×10
	Half-Value Layer—mm. Al		
A Table top	3.077	3.130	3.215
B Fluoroscopic shutter	3.065	3.087	3.155

gested above. The "narrow beam" technique utilized a 70 cm. focal-chamber distance, a 35 cm. focal-filter distance, and a 1.5×1.5 cm. aperture at the filter. The extrapolation technique was applied placing the added filters on top of the table and adjusting the field at the fluoroscopic screen, using the fluoroscopic shutters. The determinations shown in Table v are in good agreement and are appreciably lower than those shown in Table IV. One concludes, therefore, that determinations of the half-value layer on fluoroscopic apparatus are easily made by the extrapolation method without dismantling the apparatus.

SUMMARY

These investigations assume the need for the determination and reporting of a unique half-value layer. We have further assumed this to be a zero field measurement, that is, a measurement which eliminates the effects of radiation scattered from the filters. There may be local or in some cases national understanding of what constitutes an acceptable method of determination, but it would seem desirable to have some international body give consideration to the specification of a recommended method. The experimental results presented above show that it is practical to determine the zero field half-value layer by any one of three different methods: (1) narrow beam; (2) linear extrapolation of half-value layer to zero diameter of the field at the filter; and (3) apply corrections for the effects of radiation scattered from the added filters.

In measuring the half-value layer on equipment using treatment cones, the filters are best added over the end of the cone. A focal-chamber distance equal to twice the focal-filter distance should be used. For narrow beam, a small lead diaphragm should be added at the position of the filters. For the extrapolation technique an additional diaphragm is not necessary if two cone sizes are available. The size of the opening at the end of the cone is utilized in performing the extrapolation. The correction technique likewise requires no additional diaphragm. A single half-value layer determination is made and corrected for the size of the opening at the end of the cone.

In measuring the half-value layer on equipment using adjustable diaphragms, the filters are best added at the face of the diaphragm, and the focal-chamber dis-

TABLE V

COMPARISON OF HALF-VALUE LAYER DETERMINATIONS USING THREE SUGGESTED TECHNIQUES: FLUOROSCOPIC GEOMETRY

Kv. Peak	Inherent Filtration	Measuring Technique		
		Narrow Beam	Extrapolation	Correction
		Half-Value Layer—mm. Al		
85	2.5 mm. Al+table top	2.63	2.61	2.62
100	2.5 mm. Al+table top	3.06	3.03	3.04

tance should be made equal to twice the focal-filter distance. The narrow beam approximation may be made by using a diaphragm opening just large enough to enable all the chamber to receive radiation from all the target area. For the extrapolation technique the half-value layer should be measured utilizing at least two different diaphragm openings, and an extrapolation of half-value layer to zero diaphragm opening performed. Corrections may be applied to a single half-value layer determination to arrive at the zero field half-value layer. It is important to remember in this case that correction is made for the effective diameter of the field at the added filters rather than the field at the treatment distance.

In giving consideration to the specification of a recommended method for measurement of the half-value layer, it would seem advisable to take cognizance of the fact that the first half-value layer may be obtained using a high voltage and low filtration or a lower voltage and high filtration. For instance, a half-value layer of 1.0 mm. copper may be obtained using 200 kv. peak and an 0.5 mm. copper filter or 250 kv. peak and an 0.3 mm. copper filter. Thus, the same number may be used to describe two beams of different spectral distribution. Some additional specification, perhaps the second half-value layer, would seem to be needed.

E. Dale Trout
General Electric Company
4855 Electric Avenue
Milwaukee 1, Wisconsin

We wish to acknowledge the advice and criticism of the many physicists with whom we discussed this problem during the three years over which we had it under consideration. In particular, we wish to express our appreciation to Drs. L. S. Taylor and H. O. Wyckoff of the National Bureau of Standards; Dr. N. A. Baily of the Roswell Park Memorial Institute, Buffalo; Dr. A. Allisy of the Laboratoire de Dosimétrie, Paris; Dr. A. Somervil of the Radiotherapeutisch Instituut, Rotterdam, and Dr. W. J. Meredith of the Christie Hospital, Manchester.

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THE STATISTICAL PROGNOSIS IN RADIATION THERAPY*

A STUDY OF OPTIMAL DOSAGE IN RELATION TO PHYSICAL AND BIOLOGIC PARAMETERS FOR EPIDERMOID CANCER

By LIONEL COHEN, M.B., B.Ch., D.M.R.T.
JOHANNESBURG, SOUTH AFRICA

EMPIRICAL knowledge of optimal dosage procedures for the purpose of clinical radiation therapy and some of the effects of changing the quality, time and volume factors has accumulated with radiologic experience over the past several decades. Garcia[16] and Strandqvist[25] first showed in 1943 how clinical experience could be systematized by plotting graphically the results of dosage against time, and distinguishing on the graph under- and over-dosage responses. Strandqvist's analysis of the time-dose relationship, though neglecting some essential refinements, was the first attempt to derive a precise iso-effect mathematical function from clinical data. By using suitable scales the function could be transformed into a straight line easily fitted by eye so as to delimit with fair accuracy the optimal dosage range for all treatment times. The position of this line on the dose axis then gives a measure of the radiosensitivity of the tumor, while its slope is indicative of the magnitude of a specific recovery factor.

Attempts to generalize this approach have since been made by Cohen,[6] Nolan and Du Sault,[22] Andrews and Coppedge,[3] and Allen and Freed[1] for epidermoid cancer; by Costolow *et al.*[12] for uterine adenocarcinoma; and by Cohen[7] and Friedman and Pearlman[15] for mammary carcinoma. Some general hypotheses on the relative recovery of tumors and normal tissues have also been developed by Cohen and Kerrich,[11] Du Sault,[13] and Andrews.[2] The empirical relationships described have not, however, been subject to the rigorous statistical analysis required in order to compute the optimal dosage with a known degree of confidence; this is the object of the present communication.

BIOLOGIC DOSAGE FACTORS (VARIATES AND PARAMETERS)

The radiosensitivity of any tissue, or its reaction to a given dose of radiation, depends on a number of physical and biologic factors. Three of these, namely, the *quality* (photon energy), the *time* (protraction and fractionation), and the *volume* (field size and shape) factors, are subject to the control of the prescribing radiotherapist and should, in the strict statistical sense, be termed *independent variates*. Of these, the quality-function is best described in terms of the *relative biologic efficiency* (RBE or η) of the radiation in question. Used in this sense, it is convenient to take, as a standard of comparison, $\eta = 1$ when the specific ion density is minimal (say around 10 ions/μ) or the linear energy transfer (LET) equals 0.35 kev./μ. This holds true for hard γ-rays or photons with a quantum energy above 1 mev., and may be termed the radium standard for RBE.[5,8] On this standard $\eta = 1.00$ for megavoltage radiation and is correspondingly greater for conventional roentgen therapy ($\eta = 1.4$) and with superficial roentgen therapy ($\eta = 2$).

The most important of all the time variables, at least in clinical practice, is the total treatment time. Although such considerations as intensity or dose rate, whether the exposure is continuous or intermittent, and in the latter case the size, frequency and spacing of individual frac-

* The clinical investigations upon which this analysis is based were supported in part through the Farquhar Bequest Cancer Research Fund.

tions do have a perceptible influence on some reactions,[20] they are relatively unimportant. It will be shown that the over-all time in days (T) is a useful statistical variable readily incorporated in the relevant formulae.

The field size factor may be defined in terms of the area of an entrance portal or as the total irradiated volume. For biometric purposes it is expressed as the diameter (L) of a symmetric volume, or as the equivalent diameter of a cube having the same ratio of volume to bounding surface.[18]

Another three factors, which are not subject to external control but are characteristic of the tissue irradiated, also affect the reaction. In this sense they are statistical constants, strictly termed *parameters*, which include the *radiosensitivity* of the tissue or tumor in question as assessed by the dose required to produce a given response; the *recovery rate*, as determined by the amount the dose has to be increased to compensate for the effects of prolonging the treatment time; and the *diffusion constant* for the irradiated volume as estimated from the effect on the reaction of variation in field size and shape.

These six factors can be combined in an equation from which the physical dose required to produce a given reaction with any combination of technical factors can be computed.[11] This so-called *iso-effect formula* is given by:

$$D = E \cdot T^{n} \cdot L^{-q} / \eta \qquad (1)$$

where the physical dose (D) is the *dependent variate* determined by all the other factors. The over-all time (T), the field diameter (L), and the relative biologic efficiency (η) are the independent variates described. The standard radiosensitivity (E) and the recovery and diffusion exponents (n and q, respectively) are the characteristic parameters. In this way the dose required to produce any chosen reaction can be calculated for any given combination of treatment conditions.

Figure 1 shows this empirical function fitted to skin tolerance and tumor lethal doses for conventional roentgen therapy. This composite plot is derived from the skin tolerance tables of Ellis,[14] Jolles and Mitchell,[19] and Paterson,[23] and from reported epidermoid cancer curative doses as collated by various authors.[3,6,13] The best available estimates for the parameters appropriate to a variety of human tissues and tumors are given in Table 1.

The formula is, of course, applicable only to a given single tissue; it cannot, in this simple form, account for the result of interactions between two or more tissues reacting simultaneously. In clinical radiation therapy, it is precisely such a complex interaction between the tumor and one or more normal tissues which determines the success or failure of treatment. We shall, accordingly, now attempt to develop the statistical principles underlying the iso-effect formulae, taking into account the two sets of factors together, with the object of calculating that tumor dose which in given circumstances affords the greatest probability of uncomplicated cure.

Since we are now concerned with the response of at least two entities, say a tumor and its surrounding or overlying normal tissue, each with its characteristic parameters, there will be six such parameters to be considered. In addition to the three independent variates described, one must also take into account, in analyzing the joint response, the *heterogeneity factor*, *i.e.*, the ratio of maximum tissue dose to minimum tumor dose,[11] which is, in the case of external beam irradiation, a reciprocal function of the percentage depth dose at the tumor.

The dosage derived through the empirical graphic methods described, that is factor D in the formula, is, of course, a statistical estimate, an average or median value obtained from observations on large numbers of cases. The so-called tumor lethal dose is in reality the LD_{90}, that is, the dose required to cure a certain large proportion, possibly 90 per cent, of treated cases. Similarly, the skin tolerances given are average safe limits, carrying a small

TABLE I

BIOLOGIC PARAMETERS AFFECTING THE RADIOSENSITIVITY OF SOME HUMAN TISSUES AND TUMORS

Parameter	Numerical Value*	
	For 200 kv.	For >1 mev. or Ra
Median erythema dose, ED_{50}	700	$E=1,000$
Median exudative dose, or skin tolerance limit, XD_{50}	2,000	$E=3,000$
Median necrotizing dose, ND_{50}	2,800	$E=4,000$
Epidermoid cancer LD_{50}	2,000	$E=2,900$
Epidermoid cancer LD_{90}	2,500	$E=3,600$
Mammary carcinoma LD_{50}	1,270	$E=1,800$
Mammary carcinoma LD_{90}	1,600	$E=2,300$
RBE—Ra-γ's at 0.35 kev./μ	0.7	$\eta=1.00$
200 kv. at 2.5 kev./μ	1.00	$\eta=1.40$
140 kv. at 3.5 kev./μ	1.5	$\eta=2.0$
<100 kv. at 4 kev./μ	2.0	$\eta=3.0$
Recovery exponent, skin	$n=0.32\ (\pm .03)$	
Recovery exponent, epidermoid carcinoma	$n=0.23\ (\pm .02)$	
Recovery exponent, mammary carcinoma	$n=0.34\ (\pm .03)$	
Diffusion exponent, skin	$q=0.3$ to 0.4	
Diffusion exponent, tumors	$q=0$	
Standard uncertainty factor	$U=1.11$ to 1.15	

* Best available figure or averaged value from various sources quoted in text.

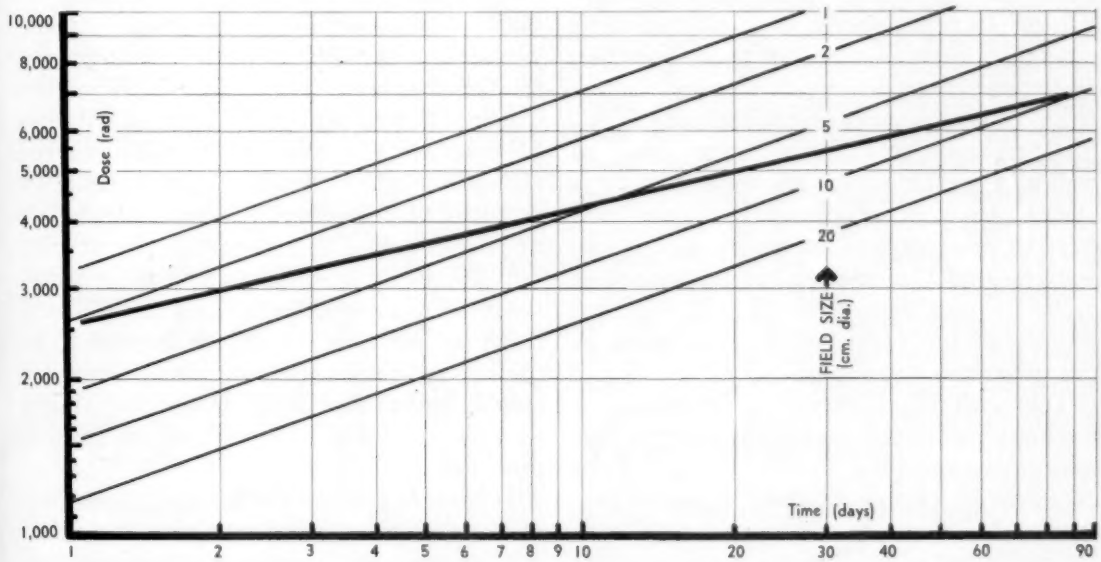

FIG. 1. Safe tolerance doses (desquamative reaction, not full tolerance limit) as functions of field size and overall time. The heavy line indicates the epidermoid cancer lethal dose (LD_{90}) for the corresponding periods. The fine lines indicate skin tolerance (2° E).

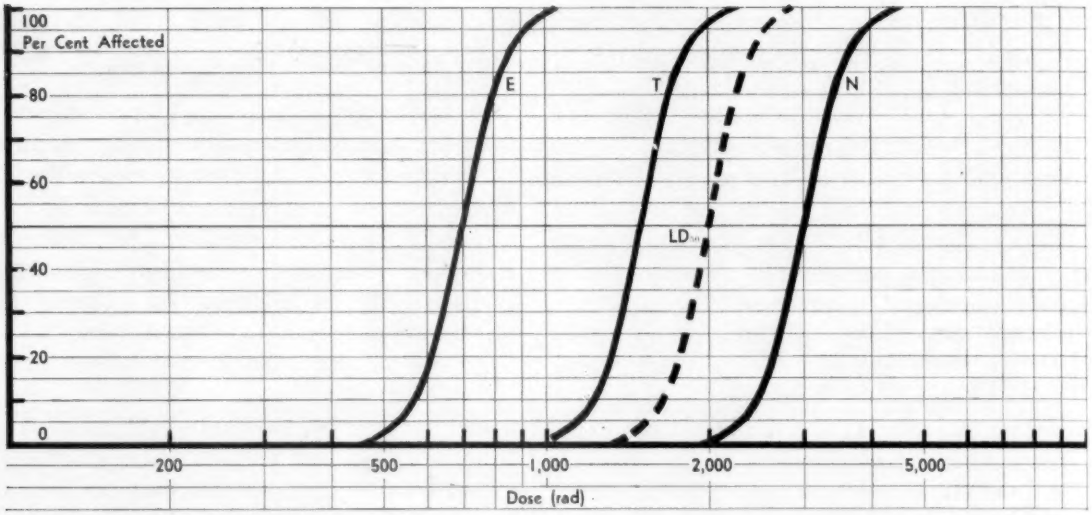

Fig. 2. Sigmoid dose-response curves for radiation reactions in human skin showing the erythema (*E*), tolerance (*T*), and necrosis (*N*) levels for a single exposure at 200 kv. on a 10 cm. diameter field. The dotted line indicates the cure rates for epidermoid cancer under the conditions specified.

risk of necrosis. This type of average ignores the fact that many individuals will respond to smaller doses and some may require considerably larger ones. It has been shown that the individual variation in radiosensitivity of both tumor and normal tissue follows a log-normal dose-response curve.[11] In other words, it is not two fixed quantities one has to compare, but two statistical distributions or sigmoid curves (Fig. 2), each having some measure of central tendency (median effective dose) as well as a certain spread (coefficient of variation). In general, the two curves will overlap more or less according to circumstances, and the relative radiosensitivities of tumor and normal tissue will vary according to the technical factors chosen in the treatment procedure.

This individual variation introduces a further parameter essential for determining optimal dosage. One needs a measure of the degree to which a particular tissue or tumor might deviate in its radiosensitivity from the estimated norm. The most suitable statistical description of this effect is given by the coefficient of variation (the standard deviation expressed as a percentage of the mean), or, as in the case of the log-normal data analyzed in this instance, by a *standard uncertainty factor* to be described.

The sigmoid dose-response curves in Figure 2 correspond to certain standard conditions of treatment, that is for particular median values of *D* in the formula. It will be seen that within narrow limits the larger the tumor dose, the greater is the probability of cure. Similarly, the larger the dose, the more severe is the reaction and the greater the risk of necrosis. It often happens in practice, and this is obvious from the curves in Figure 2, that a dose small enough to entail no risk of necrosis has little chance of effecting a cure; and conversely, it may not always be possible to approach a certainty of cure without risking a high incidence of necrosis. It will be proved that, under such circumstances, there is always a single *optimal dose* at which the probability of uncomplicated cure without necrosis is maximal.

It is evident from the foregoing considerations that the Strandqvist plot and other similar attempts at computing optimal dosage have been greatly oversimplified, and that many additional factors have to be considered before any reliable estimates of optimal dosage can be entertained.

THE THERAPEUTIC RATIO IN CLINICAL RADIATION THERAPY

The concept of a therapeutic ratio may be adopted in radiation therapy as in the case of therapeutic chemicals, so as to give a measure of the degree to which the largest safe tolerance dose exceeds the minimum effective dose. The ratio indicates the general value, and particularly the margin of safety of a given procedure. In radiation therapy, it could be defined as the ratio of tissue tolerance to tumor lethal doses. However, both these quantities are subject to individual variation and depend on technical variables and biologic parameters. In other words, the therapeutic ratio in radiation therapy is a ratio between median values, or some other acceptable measure of "position" of two sigmoid curves, corresponding to the probability of necrosis and of cure, respectively. Since skin tolerance and tumor lethal doses depend upon the many technical variables described, it is possible to control the therapeutic ratio within fairly wide limits by a judicious choice of factors, particularly the field size and the over-all time.

The computed data giving *median* values for the tumor lethal and skin tolerance doses are insufficient for the purpose of specifying optimal treatment factors in the clinical prescription, since it is necessary simultaneously to exceed the median lethal tumor dose by the largest practicable amount and yet fall short of the median necrotizing dose by the greatest possible margin. The acceptable maximum tolerance dose must carry no more than a nominal risk, say under 2 per cent, of necrosis, while the tumor lethal dose must have a similarly small risk of recurrence.

In order to estimate the actual magnitude of the therapeutic ratio in a particular case, one requires that at least eleven factors, namely, the three independent variates, the three associated parameters for both tumor and normal tissue, the standard uncertainty factor, and the heterogeneity factor, all be clearly defined and specified for the conditions of treatment.

The uncertainty factor is particularly important in computing the therapeutic ratio as it permits one to calculate the dosage required to produce greater or lesser frequencies of response from given median values. It may be used in the case of a log-normal population in the same way as the standard deviation defines the normal distribution. Algebraically, it is the antilog of the standard deviation of log dose. If the standard uncertainty factor defined in this way is designated U, then U^2 will be the 5 per cent uncertainty factor, since in any normal distribution over 95 per cent of individuals fall within two standard deviations around the mean. The factor generally has a value around $U=1.11$ to 1.14, and is approximately the same for normal tissues and tumors,[11] which means that in about 95 per cent of cases the radiosensitivity does not differ from the median value by more than a factor of U^2, approximately equal to 1.30.

It follows that increasing the LD_{50} by a factor of 1.30 would give the 98 per cent lethal dose (LD_{98}). Similarly, decreasing the LD_{50} by the same factor gives the 2 per cent lethal dose (LD_{02}). The median exudative dose (which we shall for convenience term the XD_{50}), producing the third-degree skin reaction in at least half of all cases treated, is for practical purposes identical with the generally accepted skin tolerance limit. Since $XD_{50}=\frac{3}{4}ND_{50}$ (Table 1), which is roughly equal to $ND_{50}/U^2=ND_{02}$, the incidence of necrosis to be expected through accepting the XD_{50} as a practical tolerance dose is about 2 per cent, which for reasons given below is often the irreducible minimum risk in curative radiation therapy.

Corresponging to the various levels of dosage described, the following set of therapeutic ratios can be derived and applied in the appropriate situations. If one takes the ratio of *median* necrotizing and tumor lethal doses, that is ND_{50}/LD_{50}, and designates this value θ, then the ratio of the

tolerance limit to the median lethal dose, that is XD_{50}/LD_{50}, is equal to θ/U^2. Similarly, it may be of interest to consider the ratio of tolerance and curative doses, or ND_{02}/LD_{98}, which equals θ/U^4, for if this value exceeds unity it becomes possible to deliver a dose giving a 98 per cent probability of tumor regression with no more than a 2 per cent risk of necrosis, so that the total probability of uncomplicated cure approaches a theoretical maximum of 96 per cent.

It will be realized that there is in this reasoning one assumption which may not remain valid under all circumstances. It was assumed that the tumor and normal tissues concerned in assessing the therapeutic ratio receive the same dose of radiation. In practice, of course, the overlying skin, or some other tissue, frequently receives a greater dose than that reaching the tumor. This heterogeneity will, in effect, diminish the therapeutic ratio and worsen the prognosis. To allow for this factor, another type of therapeutic ratio is required: namely, the ratio of medians corrected for heterogeneity, that is $ND_{50}/H.LD_{50}$, or θ/H, where H is the heterogeneity factor as defined previously. The importance of this particular ratio lies in the fact that the prognosis, expressed as a probability, can be shown to be a mathematical function of this factor.

The probability of cure at any given *tumor dose* depends on the factor by which that dose exceeds the LD_{50}. Simple statistical theory gives this probability in terms of the normal deviate (δ) in the expression.

$$D = LD_{50} \cdot U^{\delta} \qquad (2)$$

where D is the tumor dose and U the standard uncertainty factor as defined previously. Taking the skin tolerance limit XD_{50} as the maximum permissible dose, it follows that the tumor dose cannot exceed

$$D = XD_{50}/H \qquad (3)$$

where H is the heterogeneity factor. From these two equations

$$H \cdot U_t^{\delta} = \frac{XD_{50}}{LD_{50}} = \theta/U_s^2 \qquad (4)$$

where U_s and U_t are the uncertainty factors for skin and tumor responses, respectively. It may be assumed that $U_s = U_t$, which is approximately true in most instances, and the expression (4) is then simplified to read

$$\theta/H = U^{2+\delta}$$

whence

$$\delta = \frac{\log \frac{\theta}{H}}{\log U} - 2. \qquad (5)$$

Since the divisor in equation (5) is constant for any given tumor species, δ is directly proportional to $log(\theta/H)$. It is then possible to calculate δ, and determine the associated probability level. The probability of cure corresponding to any given value of δ can be obtained from statistical tables of the normal deviate or from the area of the normal curve. It will be noted that $\delta = 0$ corresponds to a cure rate of 50 per cent; $\delta = 1$ to 84 per cent; and $\delta = 2$ to 97.7 per cent. In this way a definite prognosis as far as the primary growth is concerned can be assigned to any tumor the parameters of which are specified, treated over a given period to the limits of tissue tolerance.

ESTIMATION OF THE STATISTICAL PROGNOSIS

The concept of prognosis as applied to the local disease can be given a precise quantitative meaning in the sense of an estimated probability of uncomplicated cure with a given treatment regimen. It can be computed as the probability of cure at the dose given, *minus* the probability of necrosis at that dose. Since both probabilities are sigmoid curves, this difference should be a monophasic function with a well-defined maximum (Fig. 3 and 4). In other words, there must exist a particular dose at which the probability of cure, that is of tumor regression without necrosis, is maximal. It will be shown that this *optimal*

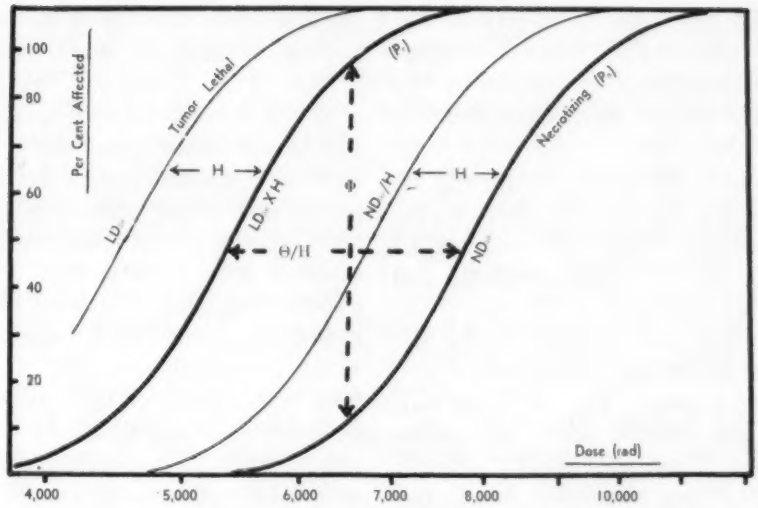

FIG. 3. Dosage response curves for epidermoid cancer and normal skin treated at 200 kv., 10 cm. diameter field, 26 days over-all time, heterogeneity factor 1.2. θ is the therapeutic ratio and Φ the prognosis. Curves indicate the probability of tumor regression (P_r) and necrosis (P_n).

dose lies between the two median values and tends to approach their geometric mean. The prognosis can thus be assigned a percentage probability ranging from zero at low dosage, through a maximum or optimal dose and down to zero again at grossly excessive dosage.

It is apparent from the sigmoid curves in Figure 3 that increasing the tumor dose should increase the probability of cure. Also following a similar sigmoid curve, the risk of necrosis increases continuously with increasing tissue dose. Observed cure rates, at least for epidermoid cancer, have in fact been found by Cohen and Kerrich[11] to follow the sigmoid curve very closely with the exception of the extreme upper limb, where concomitant with the increasing risk of

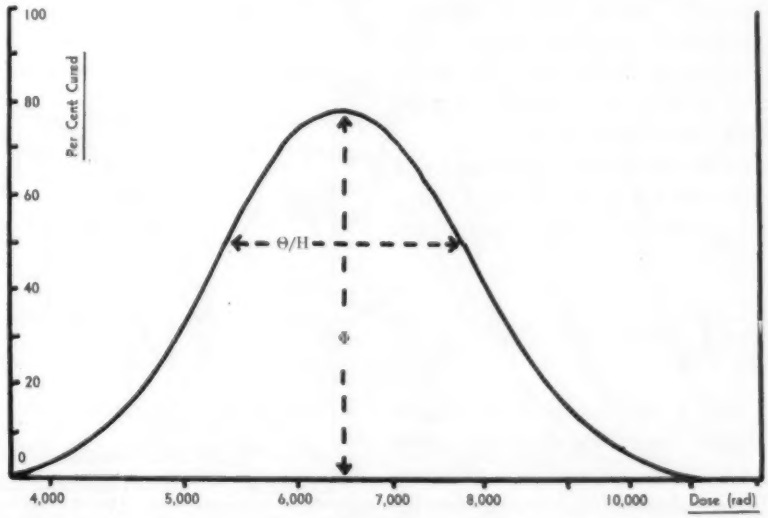

FIG. 4. Prognosis as a function of dosage and therapeutic ratio, $\Phi = P_r - P_n$, that is the difference between the two curves in Figure 3. Manifestly, the optimal dose of 6,600 rad gives 80 per cent uncomplicated cures, 10 per cent recurrence, and 10 per cent necrosis.

necrosis, a distinct downward trend appears. This is presumably a manifestation of the supralethal effect (Paterson[23]), appearing as the limits of normal tissue tolerance are exceeded.

Since necrosis is, therefore, not merely an undesirable complication of overdosage, but is also associated with a tendency to recurrence of the irradiated tumor, the true dosage-response curve for the probability of local cure is a function of the difference: (probability of regression, P_r)—(probability of necrosis, P_n). If these two probabilities are stochastically independent, the *prognosis* or probability of cure $\Phi = P_r(1-P_n)$. If, on the other hand, the two functions are correlated, the prognosis approaches $\Phi = P_r - P_n$. The latter seems the more likely alternative, since the spread of the curve is due, at least in part, to variation in dosage attributable to fluctuations in output of the radiation source, which would affect both skin and tumor simultaneously. At the upper range of curability, with which we are concerned in practice, there is little difference between the alternatives, though the latter, somewhat underestimating the cure rate associated with a given procedure, tends to err on the side giving the greater margin of safety. In either instance, the estimated prognosis follows a symmetric monophasic curve (Fig. 4) with a single maximum the position of which is readily computed and indicates the theoretic optimum dose.

Assuming the second alternative and the log-normal distributions previously suggested, the prognosis may then be represented as:

$$\Phi = \frac{1}{\sigma\sqrt{2\pi}} \int_{-\infty}^{\zeta} e^{(\lambda-\xi)^2} - e^{(\nu-\xi)^2} \cdot d\xi \qquad (6)$$

where ζ, λ, ν, and σ respectively represent the logarithms of the given dose (D), the median tumor lethal dose (LD_{50}), the median necrotizing dose (ND_{50}), and the standard uncertainty factor (U) previously described. It then follows that the curve reaches its maximum when $\lambda + \nu = = 2\zeta$, that is when the given tissue dose is the geometric mean between the LD_{50} and the ND_{50}.

While the *position* of the peak indicating the optimal dose for a given set of treatment factors can be determined in the foregoing manner, the *height* of the peak, representing the probability of cure at the optimal dose calculated in this way, is dependent on the degree of separation between the tumor lethal and tissue necrotizing dosage curves (Fig. 3), being therefore, a function of θ/H. The relationship between the prognosis (Φ) and the therapeutic ratio (θ) is illustrated in Figure 4, Φ and θ being respectively the vertical and horizontal axes of the area enclosed by the two relevant sigmoid curves (heavy lines in Figure 3). To any given value of θ/H there corresponds a definite maximum prognosis (Φ max.). The function can be solved by using tables of the probit transformation, so that the prognosis or chance of cure, given the optimal dosage appropriate to the circumstances, can be computed. The relationship of Φ max. to θ/H is shown graphically in Figure 5. It will be noted that a value of $\theta/H = 1.5$ corresponds to a possible cure rate of 90 per cent.

The existence of specific optimal doses giving maximal cure rates, both larger and

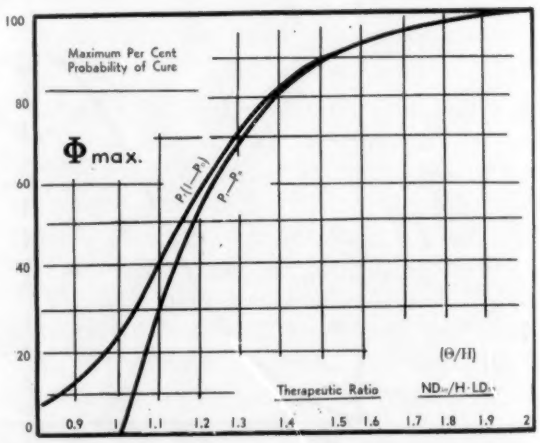

FIG. 5. Prognosis as a function of therapeutic ratio, when regression and necrosis are assumed to be stochastically independent, $P_r(1-P_n)$; or fully correlated, $(P_r - P_n)$.

smaller doses giving inferior results, has been reported in several clinical series and confirms the general validity of the foregoing theory. In their studies on dosage control for carcinoma of the cervix, Tod[26] and Garcia[16,17] first demonstrated the existence of an optimal dosage level for this tumor. Subsequently, similar monophasic response curves were obtained by Nolan, Costolow and Du Sault[21] and by Paterson[24] in their independent series of uterine cancers.

While the exact magnitudes of the optimal doses in other types of tumor and other situations have yet to be determined empirically, it should be possible, using the foregoing methods, to compute these quantities theoretically. Such values should, pending their experimental verification, furnish clinical dosage standards giving the best results obtainable with present day techniques.

COMPUTATION OF THE OPTIMAL DOSE IN CLINICAL PRACTICE

The validity of the theoretic analysis may also be tested by comparing the computed cure rates for some common tumors with the corresponding empirical data established through clinical experience. In Figure 6 are shown a series of prognostic curves, derived in the same manner as that of Figure 4, for epidermoid cancer treated under a variety of conditions with fields of 2, 5, 10, and 20 cm. diameter, over-all times of 1 day, 1 week (5 days) and 1 month (26 days); and a heterogeneity factor of 1.2 in each instance. The following facts, all well-established from clinical experience, emerge directly from the computed curves and thus seem to confirm the validity of the calculations.

With fields not more than 2 cm. in diameter, satisfactory cure rates are obtainable with single treatments, the optimal dose being 2,500 rad (maximum) with superficial therapy. With larger fields, longer treatment times are desirable; a week is required for fields up to 5 cm. in diameter and over a month with 10 cm. diameter fields. It is to be expected, in fact, that the optimum over-all time should vary roughly as the cube of the field diameter, equivalent therapeutic ratios obtaining with fields of 2.5 cm. treated in 1 day, 5 cm. in 1 week, and 8 cm. in 1 month. For 1 week the optimal dose is seen to be 4,500 rad with high-voltage roentgen rays or 7,000

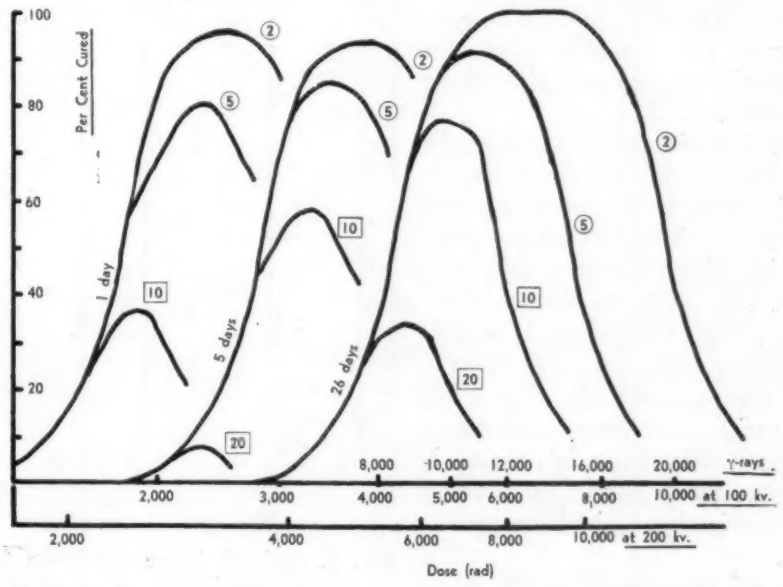

Fig. 6. Probability of cure of epidermoid cancer as a function of dose, time, field size, and quality.

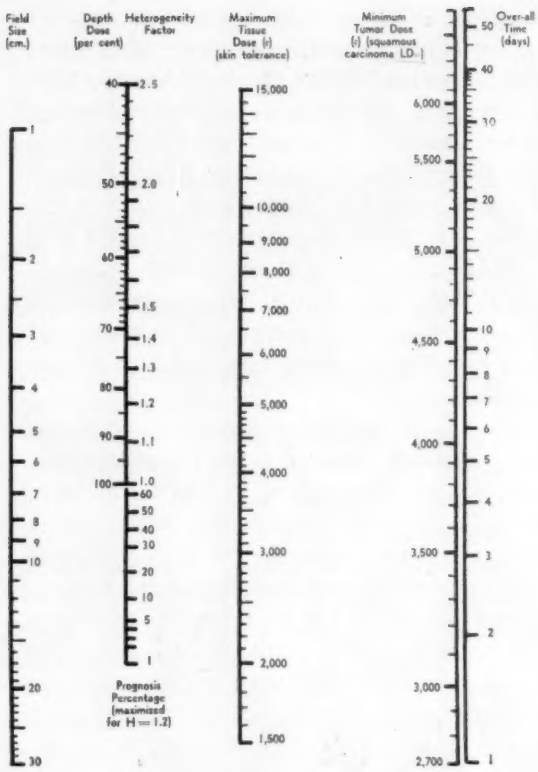
Field Size (cm.)
Depth Dose (per cent)
Heterogeneity Factor
Maximum Tissue Dose (r) (skin tolerance)
Minimum Tumor Dose (r) (squamous carcinoma LD50)
Over-all Time (days)
Prognosis Percentage (maximized for H = 1.2)

FIG. 7. Optimal dosage nomogram for 200 kv. roentgen therapy.

rad with radium, and for 1 month about 6,500 rad with high-voltage roentgen rays. Since the estimates were based on a heterogeneity factor of 1.2, absolute minimum tumor doses may be 20 per cent below these computed maxima.

Since all the foregoing predictions are in conformity with established practice, it is probably justifiable to generalize the method so as to permit one to compute the optimal dose for other clinical problems of the same type. The practical procedure by which this figure can be derived is as follows, taking the parameters from Table 1:

1. Physical arrangement of one or more fields giving a satisfactory percentage depth dose, noting the quality factor (η), the equivalent field diameter (L), and calculating from the relevant isodoses, the heterogeneity factor (H).

2. Selection of an approximately suitable time factor (T) as described, subject to adjustments if the therapeutic ratio is not satisfactory.

3. Estimation of the median necrotizing dose (ND_{50}) by substituting in the iso-effect formula the values:

$$\frac{4{,}000}{\eta}(T/L)^{0.33},$$

and of the median tumor lethal dose (LD_{50}), using, with epidermoid cancers, the formula:

$$\frac{3{,}000}{\eta}\cdot T^{0.22},$$

and in breast cancer

$$\frac{1{,}800}{\eta}\cdot T^{0.34}$$

(see Table 1).

4. Taking the ratio $ND_{50}/H.LD_{50}$ as an estimate of the therapeutic ratio (θ/H). If

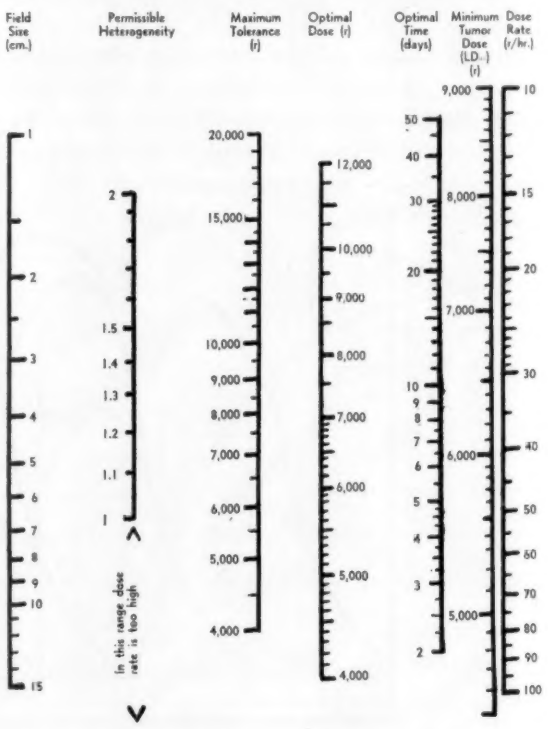

FIG. 8. Optimal dosage nomogram for radium or other continuous γ-ray applications.

this radio does not exceed 1.5, corresponding to a prognosis bettering 90 per cent (Fig. 5), one of the following adjustments is indicated: (a) changing the physical factors if possible for greater homogeneity; (b) reducing the field-size, if feasible, possibly using grids or sieves; (c) prolonging the over-all time by a significant factor.

5. Taking the geometric mean between ND_{50} and $H.LD_{50}$ which gives the optimal maximum tissue dose. Alternatively, the geometric mean between ND_{50}/H and LD_{50} gives the optimum value for the minimum tumor dose.

CLINICAL DOSAGE NOMOGRAMS

In the case of squamous cell carcinoma treated radically, that is with the object of achieving the highest practicable cure rate, the arithmetic procedure described in the foregoing section can be facilitated by using the three nomograms to be described below. The principles used in designing this type of nomogram have been described *in extenso* elsewhere.[6] Many details in the construction of these particular diagrams have been modified in the light of more recent data.

The first nomogram (Fig. 7) is designed

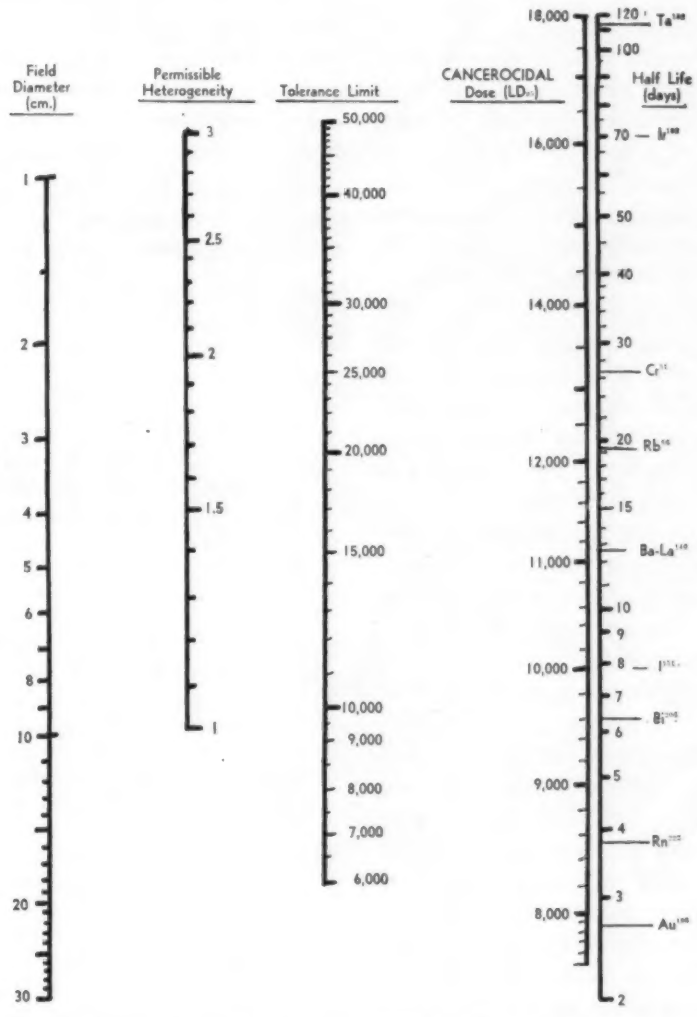

Fig. 9. Optimal dosage nomogram for permanent implants of radioactive sources.

for use with conventional 200 kv. roentgen rays delivered in equal daily fractions. A single line passing through the figure gives related values on all the scales simultaneously. Thus, if a rule is set on the field size suitable for a given lesion and on the heterogeneity factor appropriate to the conditions of treatment, it will intersect the time scale at a point indicating the most suitable over-all time, and the two dose scales at the skin tolerance and tumor lethal doses for the conditions used. If all 5 scales cannot be intersected, as happens with large fields or short treatment times, the proposed treatment in unsuitable for the case in question.

The second nomogram (Fig. 8) is designed for continuous irradiation with hard γ-rays ($\eta = 1.00$) such as would obtain with radium applicators and implants, or with isotopes of similar quality having half-lives long enough to ensure that no significant reduction in dose rate occurs during the exposure period. This includes Co^{60} and Ta^{182}, though, with the rather softer radiations of Ir^{192}, Cr^{51}, and I^{131}, a correction for RBE might be required. Here again a single line across the figure gives all the related factors simultaneously. The dose rate and optimal dose scales are computed for optimal doses *averaged* over the irradiated region, and are thus compatible with the Paterson-Parker system of radium dosage tables. If the radium or isotope is correctly distributed, the corresponding maxima and minima, which depend on the heterogeneity factor, will fall within practicable limits.

The third nomogram (Fig. 9) is applicable to permanent implants of radioactive sources, where the time factor is determined by the disintegration rate of the isotope chosen. The technical factors underlying this choice and the theoretic basis for the dosage data used in constructing this nomogram have been described elsewhere.[10] It is apparent from the figure that the protracted irradiation obtained with the longer-lived sources such as Ta^{182} has, in certain difficult situations, very definite advantages over conventionally used materials and procedures.[9]

SUMMARY

The principles of biologic dosimetry, insofar as optimal tissue and tumor doses are affected by appropriate variates and parameters, are reviewed, and a composite iso-effect formula applicable to human skin and cancer is derived. Applying this formula to both skin and tumor simultaneously, the therapeutic ratio is computed with due regard to individual variance and the various possible combinations of technical factors. It is shown that the prognosis, in a strict statistical sense, is a function of this ratio, and that in most cases a single optimal dose giving the greatest theoretic probability of uncomplicated cure can be calculated from these figures. Some practical optimal dosage nomograms are derived, and it is concluded that the method could be developed so as to devise effective prescriptions for clinical cancer therapy.

Radiation Therapy Department
Johannesburg General Hospital
Johannesburg, South Africa

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ISODOSE DISTRIBUTION AND TREATMENT PLANNING WITH ELECTRONS OF 20–35 MEV. FOR DEEP-SEATED TUMORS*

By J. OVADIA, Ph.D., *and* E. M. UHLMANN, M.D.
CHICAGO, ILLINOIS

THE high energy electron unit at Michael Reese Hospital consists of a 10 foot linear accelerator which is essentially a copy of the Mark II Lineac developed at Stanford University, and a magnet system which analyzes the energy spectrum of the electrons emerging from the accelerator and deflects them into the patient treatment room.

PHYSICAL CHARACTERISTICS

Originally, as described by Hsieh and Uhlmann,[3] a defocused electron beam was used at the irradiation site and its cross section was controlled by changing the focal length of the magnet. This method made excessive demands on the frequency stability of the Rf power which is used to accelerate the electrons and, therefore, was changed to an arrangement briefly described elsewhere[4] and illustrated schematically in Figure 1.

A toroid coil through which the beam passes undisturbed and the associated electronic circuitry[1] are used to measure continuously the total current emerging from the accelerator; its average value is approximately 0.5 microampere. This device has proved to be very useful in obtaining an output beam from the accelerator when the operation of the machine is started; it has also been valuable in studying the effects of various parameters of the accelerator on the electron pulse shape and electron pulse length.

A lead foil, 0.4 mm. thick, located immediately beyond the 135° deflecting magnet provides enough scattering to produce a uniform field 18 cm. in diameter at the irradiation site, 1.2 meters away, for energies up to 35 mev. Lead was chosen because of its high atomic number, since for a given amount of beam spreading, it produces a minimal penetration loss (in our set-up about 5 mm. in tissue). The maximum dose to the patient arising from the high energy roentgen rays generated in the lead scatterer has been estimated by making measurements in phantoms beyond the range of the electrons. For 35 mev. electrons, this dose is between 2 and 3 per cent of the electron dose, which is considered to be negligible.

For therapeutic application, electrons varying in energy from 10 mev. to 35 mev. have been used. The proper electron energy is determined by choosing the required current on the analyzing and deflecting electromagnets. Two cavity ionization chambers on each side of the treatment tube are connected to a difference amplifier giving a zero reading on a meter at the control panel when the beam is properly centered. The incorporation of this circuit was considered advisable to insure exact centering of the beam at all energies.

A transmission ionization chamber intercepts the entire beam; it is connected to a wide range exposure rate meter and ionization current integrator. The actual dose to the patient is evaluated by calibrating the integrated current of the transmission chamber against a Victoreen thimble chamber placed at the center of a 3 cm. block of lucite. This particular thickness was chosen because the electron depth dose curve is uniform to within 2 per cent at the location of the Victoreen thimble chamber for electron energies ranging from 10 to 35 mev.

Interchangeable collimators, composed of

* From the Tumor Clinic of Michael Reese Hospital and Medical Center, Chicago 16, Illinois.
Presented in part at the IX International Congress of Radiology in Munich, July 23–30, 1959.

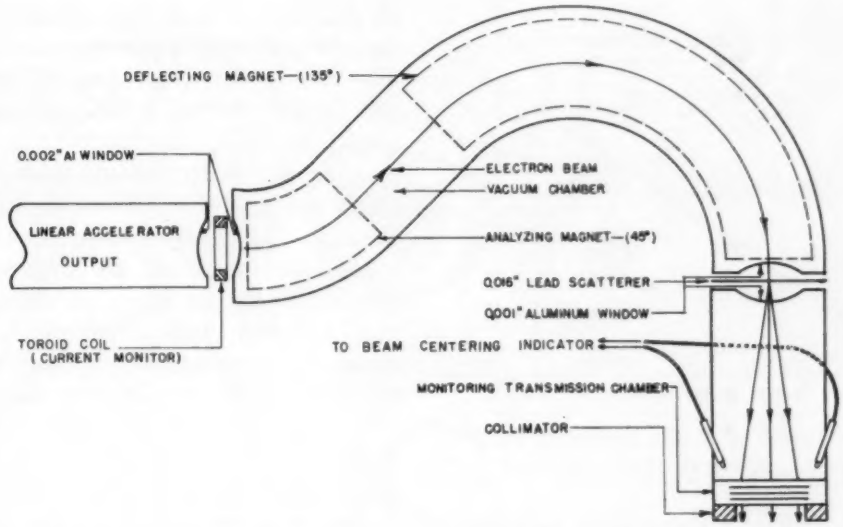

Fig. 1. Schematic diagram of auxiliary apparatus used to adapt linear accelerator for electron therapy.

2.5 cm. aluminum and 1.25 cm. brass, are sufficient to stop the electrons at the highest energy used. Changes of field size present no problem since the weight of the individual collimators is less than 5 kg.

A photograph of the therapy room appears in Figure 2 and shows the treatment tube with the collimator in position. Additional collimators for various field sizes can be seen on the table.

INVESTIGATIONS OF DOSE DISTRIBUTION

The actual determination of dose distribution was carried out with Kodak Industrial AA Film, embedded in unit density pressdwood. The film density was measured on a Macbeth Ansco densitometer using a 1 mm. light spot. The normal procedure consisted in exposing the films at a low exposure dose rate, of the order of 1 rad/min., for a total dose of approximately 2 rads. A few dose distributions were obtained at typical dose rates used in therapy (60–100 rad/min.) to ascertain that irradiation at relatively low intensity does not change the isodose distribution. The dose delivered to individual films could be set to an over-all accuracy of 2 per cent by means of the current integrator. For high energy electrons, it was found that the net density of Industrial AA Film (observed density minus background fog) varies linearly with the dose, up to a density of 2.4 used in this work, as demonstrated in Figure 3, where the six points represent six films developed simultaneously under controlled conditions; these observations are in good agreement with a more extensive study of film dosimetry for high energy electrons which was carried out at Memorial Hospital in New York and reported by Dr. Dutreix[2] from the Institut Gustave Roussy.

Fig. 2. Photograph of therapy room. Note treatment tube with collimator in position, treatment bed and series of collimators.

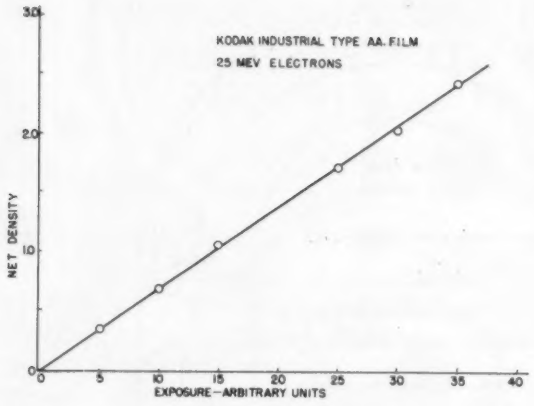

FIG. 3. Net density of Kodak Industrial Type AA Film vs. exposure with 25 mev. electrons.

A special effort was made to investigate the depth dose curves in the first 2 cm. of the distribution, since there has been some discrepancy in the measurements as published from various institutions. In particular, a reduced darkening of the film has been reported to occur when the electrons travel parallel to the film, as compared to film exposed perpendicular to the beam. This effect would be most easily observable near the surface of a phantom in which a film is embedded parallel to the beam; here the electrons are still moving relatively parallel to the film, whereas at greater depths, the contribution of scattered electrons tends to mask such an effect. A conceivable source of discrepancy between different observers arises from the contributions to the dose near the surface from low energy radiation scattered by the collimators and various supporting structures and also from electrons expelled from the various foils of the transmission ionization chamber. It is therefore not sufficient to specify only the electron energy and field size, but the geometric relations of these additional scatterers must also be given.

Some results of our investigations are illustrated in Figure 4, which shows central axis depth dose curves in lucite (used for its good mechanical properties) for 25 mev. electrons. Curve (*a*) was obtained with a film parallel to the beam when no particular effort was made to compress the lucite phantom. Curve (*b*) represents similar conditions with a tightly compressed phantom. The curves (*c*) were obtained by varying the distance between the phantom and the collimator from contact to 15 cm., thereby altering any contributions from low energy radiation scattered from the collimator. Finally, the crosses represent measurements obtained from six films placed perpendicular to the beam at various depths and exposed and developed simultaneously. It appears that neither the angle of the film nor the proximity to the collimator affect the distribution near the surface. Some of the discrepancies in film work might thus have arisen from an inadequate compression of the phantom around the film, especially near the surface, where small air pockets may exist unless a special effort is made to avoid them. We have ob-

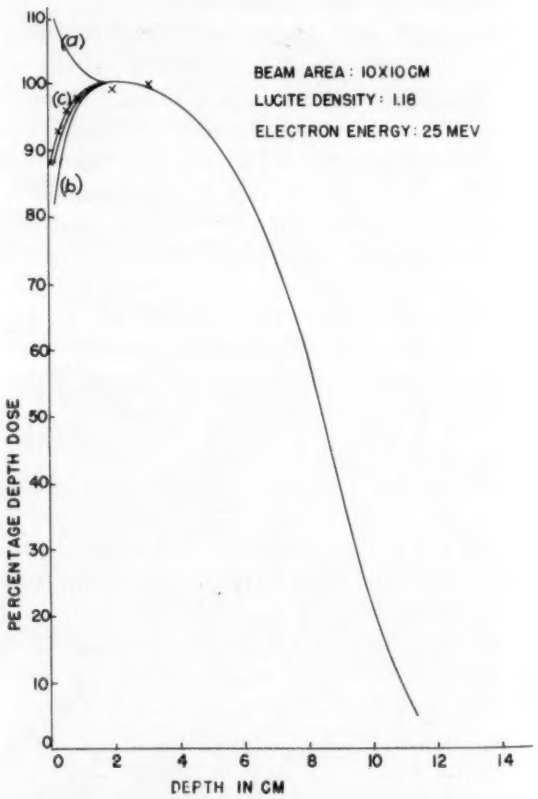

FIG. 4. Central axis depth dose curves produced in lucite by a 10×10 cm. beam of 25 mev. electrons. (Films exposed under various conditions. See text.)

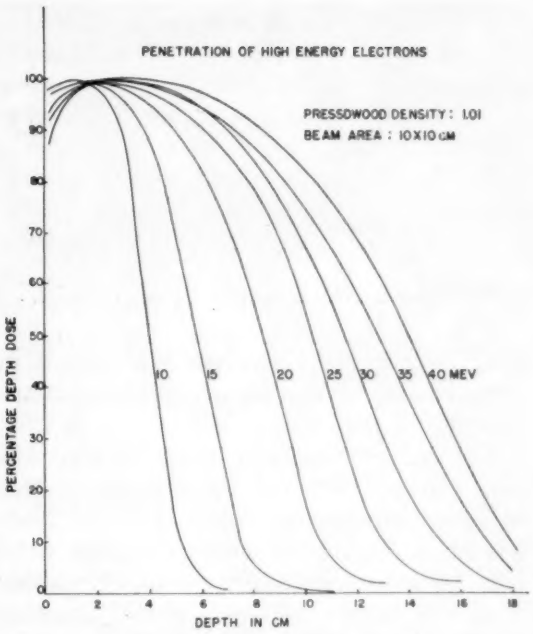

Fig. 5. Central axis depth dose curves in pressdwood for electrons of various energies. (Reproduced by permission from *Radiology*.)

served, however, that the three 0.001 inch aluminum foils of our transmission ionization chamber, located approximately 8 cm. from the phantom, increase the dose at a depth of 2 mm. by approximately 10 per cent, that is, from 80 per cent to 90 per cent for 33 mev. electrons.

A typical set of central axis depth dose curves for electron energies ranging from 10 to 40 mev. for a 10×10 cm. field, obtained under conditions illustrated in Figure 1, appears in Figure 5.

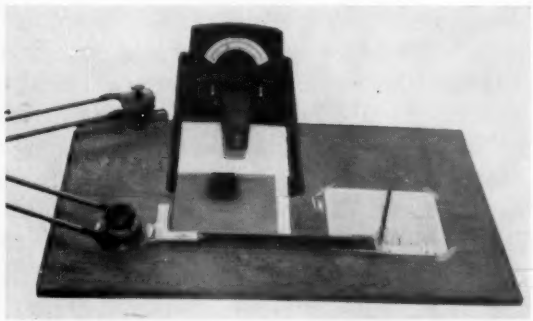

Fig. 6. Adaptation of drafting machine to densitometer for rapid and convenient tracing of isodose distributions.

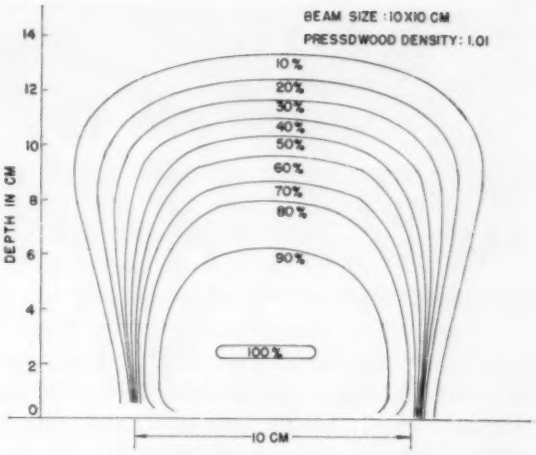

Fig. 7. Isodose distribution of 25 mev. electron beam in pressdwood. (Reproduced by permission from *Radiology*.)

To facilitate the determination of isodose distribution, it was found practical to use a drafting machine in connection with the densitometer as shown in Figure 6. Two typical isodose distributions are presented in Figures 7 and 8.

TREATMENT PLANNING

In dealing with tumors located near the surface, single fields, or fields lying adja-

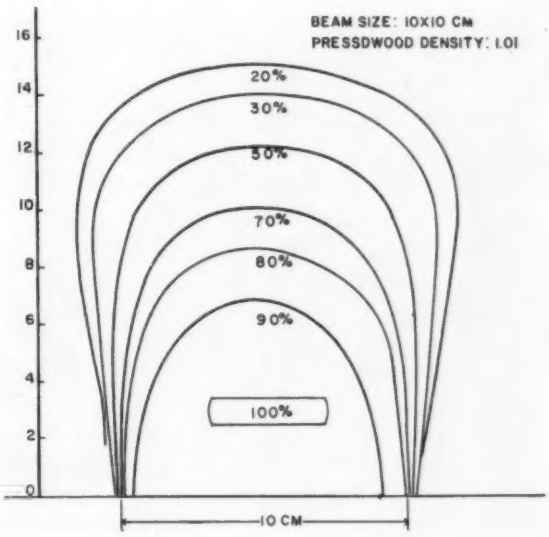

Fig. 8. Isodose distribution of 35 mev. electron beam in pressdwood. (Reproduced by permission from *Radiology*.)

FIG. 9. *Left*: Penetration of 10 mev. electrons. *Right*: Residual penetration beyond 2.5 cm. of lucite.

cent to each other, are used. The absence of a sharp lateral edge as the beam penetrates tissue permits the juxtaposition of several fields without the danger of hot spots or unirradiated tissue which might arise from slight misalignment of the various fields.

In the therapy of tumors requiring a very shallow dose distribution, as for instance in mycosis fungoides of the skin, a block of lucite of appropriate thickness is placed above the skin for the purpose of utilizing only the residual electron range at the lowest energy (10 mev.) at which our accelerator delivers a satisfactory output (50 r/min.). This is illustrated in Figure 9 where the penetration of 10 mev. electrons in unit density pressdwood is shown on the left; at the right the residual range in pressdwood, beyond 2.5 cm. of lucite, is apparent.

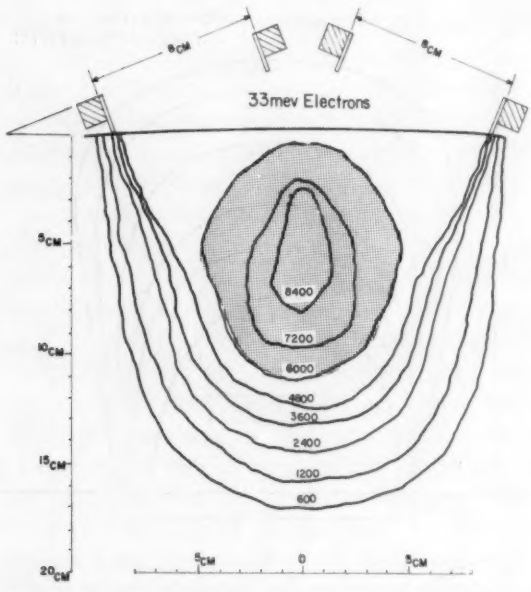

FIG. 10. Treatment plan for carcinoma of bladder.

For deeper tumors, a favorable distribution can be obtained by the use of two oblique, converging fields. This is illustrated in Figure 10 where the treatment plan for a carcinoma of the urinary bladder is shown with utilization of two anterior fields only. In this plan an effective dose is delivered to the urinary bladder, the skin tolerance is not exceeded, and the rectum and the bones of the lower spine are spared.

Centrally located tumors are irradiated by utilizing two fields aimed from opposite directions; the energy is selected in such a way that the two beams overlap the thickness of the tumor but produce no exit dose. This is illustrated for a tumor of the nasopharynx in Figure 11.

It is apparent that the dose distribution which can be obtained through bilateral irradiation with electrons of suitable energy is superior to cobalt 60 gamma rays or supervoltage roentgen rays under similar conditions. The use of 22 mev. roentgen rays produces an equally low skin dose, but a much larger integral dose to healthy tissue. The utilization of additional fields, or the use of rotation therapy with high energy roentgen rays or cobalt 60 gamma rays, would automatically increase the integral dose to healthy tissue for a given tumor dose.

The advantages of electron irradiation of centrally located tumors by opposite portals are seen in the following factors: 1. The integral dose to healthy tissue is always a

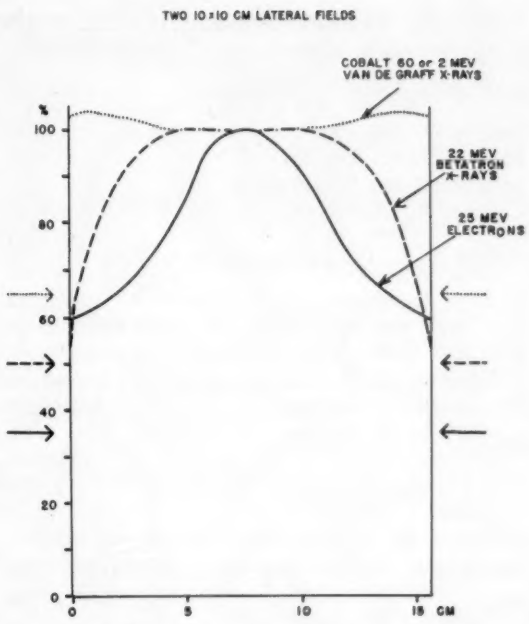

Fig. 11. Comparison of central axis distribution resulting from bilateral irradiation of nasopharynx with 25 mev. electrons, 22 mev. roentgen rays and cobalt 60 gamma rays. (Reproduced by permission from *Radiology*.)

minimum when the least number of fields is used. 2. Although the surface dose with only two portals is high (of the order of 4,000 r to 5,000 r), the skin reactions clear up readily with the treatment schedule used (1,000 r tumor dose per week). 3. The probability that the volume intended for therapy is actually irradiated, day after day, is highest when only two portals are used and the patient is treated alternately in a prone or supine position with a vertically downward beam. This is particularly important in the treatment of the esophagus, the depth of which within the patient varies considerably along its length; treatment with multiple ports or rotation therapy can be reliably carried out only with the aid of elaborate positioning devices and time consuming procedures.

A satisfactory dose distribution within centrally located tumors can best be obtained when the anterior and posterior surfaces are nearly parallel. This can be easily achieved by using lucite wedges of proper angle. The actual dose to the skin is thereby increased by approximately 10 per cent since the buildup in the depth dose which occurs near the surface (see Figure 5) takes place within the lucite wedge. Moreover, the use of these wedges effectively places the opposite chest wall beyond the range of the electrons and eliminates the exit dose which would unnecessarily increase the skin reaction.

In the treatment of lung cancer, an additional problem arises from the nonuniform density of the tissues within the irradiated field. The low average density of lung tissue produces an exit dose in certain portions of the opposite chest wall for electron energies required to treat deep seated tumors. A reduction of the energy of the beam provides no satisfactory solution, since the originally selected high energy is required for part of the field, where the density is near unity. The difficulty can be easily overcome by placing properly shaped lucite absorbers over the patient at the entrance field; these reduce the electron range in tissue under the absorber and eliminate the exit dose over the entire field. Before the absorbers can be constructed, the distribution of exit dose for individual patients is evaluated; for this

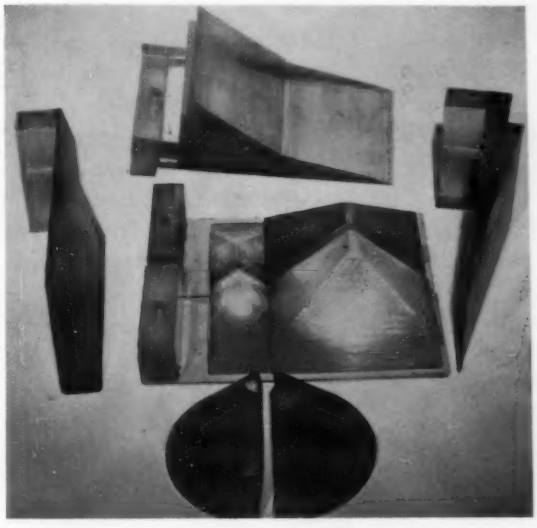

Fig. 12. Typical lucite absorbers and wedges used to modify electron dose distributions within patients.

purpose, films are exposed at several electron energies to measure those electrons which have traversed the patient. These measurements reveal the effective unit density thickness of the patient over the entire field, and determine the shape of the required additional absorbers. Typical wedges and absorbers are shown in Figure 12.

SUMMARY AND CONCLUSION

The above report of our experience with high energy electrons gives some impression of the problems which have arisen in the utilization of this modality, describes some of the solutions which we have found, and also gives an indication of the flexibility of high energy electrons in therapeutic application. Their wide range of penetration, mainly dependent on the energy, the facility in obtaining practical field sizes, and the ease of altering and modifying the distribution allow for a wide range of variations in individual patients and make therapy with high energy electrons practical and highly attractive.

Jacques Ovadia, Ph.D.
Michael Reese Hospital
29th Street and Ellis Avenue
Chicago 16, Illinois

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Vol. 84, No. 4

THE DESIGN OF A SECOND COBALT 60 UNIT, BASED ON THE EXPERIENCE ACQUIRED WITH 1,000 PATIENTS TREATED WITH THE FIRST UNIT*

By GILBERT H. FLETCHER, M.D., ERNEST J. BRAUN, M.D.,† E. B. MOORE, B.S., *and* EARL VAN ROOSENBEEK
HOUSTON, TEXAS

THE clinical advantages of supervoltage roentgen therapy have gradually become better defined, as a great variety of supervoltage equipment has become available since the first million volt roentgen-ray generators were put into use in the early 1930's.

Skin sparing, a quality shared with the original teleradium units, is only one of the characteristics of supervoltage roentgen therapy. Adequate irradiation of deep-seated tumors, such as the squamous cell carcinomas of the oropharynx and the tumors of the urinary bladder, has become feasible because of the considerable increase in depth dose. In the instance of the bladder tumors, cancerocidal doses can be given without excessive skin and systemic reaction and also without excessive organ discomfort, in contrast to the extremely poor tolerance of the bladder to conventional voltage irradiation. The explanation of the increased organ tolerance is not complete, but is probably on the basis of less energy dissipation in the adjacent structures, thus allowing recovery from surrounding undamaged tissues.

Because of the better systemic tolerance due to a smaller integral dose, new areas of therapy with segmental irradiation of the torso are open to investigation in the lymphomas, ovarian cancers, and extensive metastases, for instance from testicular tumors, etc.

Supervoltage roentgen therapy has four main characteristics: (1) skin sparing; (2) considerable increase in depth dose; (3) minimal integral dose and also minimal energy dissipated around the beam; and (4) decrease in differential bone absorption, which is attained at the cesium 137 0.6 mev. level. The 2 mev. roentgen-ray beam, which fulfills all four requirements, can be taken as a norm with which beams from other roentgen-ray generators or teletherapy units can be compared.

The multimillion volt roentgen-ray generators, such as the 22 mev. betatron, offer a still greater increase in depth dose and depth of maximum build-up, but as voltage increases so does the narrowness of useful intensity. These two characteristics make possible further radical changes in treatment planning. For instance, the use of lateral portals for tumors of the pelvis is not advisable with the 2 mev. beam because of comparatively poor depth dose yield, whereas very effective depth doses are obtained with the 22 mev. betatron beam. Four portals around the body (one anterior, one posterior, and two lateral) allow very high dose total pelvic irradiation without excessive doses to the subcutaneous tissues, muscles and intestines. The deeper electronic build-up is a disadvantage in tumors closer to the skin. Segmental therapy with multimillion volt generators is not possible because maximum field size is 15 cm.

The availability of cobalt 60 and, more recently, cesium 137 has occasioned a great variety of equipment designs. The original cobalt 60 units were designed to have beams equivalent to those of the 2 mev. roentgen-ray generators.[2,3,4,5,12] Maximum flexibility of field shaping and minimal

* From the Section of Radiotherapy and the Department of Physics, The University of Texas M. D. Anderson Hospital and Tumor Institute, Houston, Texas.
† Present address: Department of Radiotherapy, White Memorial Hospital, Los Angeles, California.

penumbra were the prime objectives of the collimator.[4] All units, provided care is taken to minimize electron contamination,[7,8,9,10] have a satisfactory skin sparing effect. However, many of these units have beams otherwise similar to 3–5 mm. Cu half value layer beam roentgen-ray generators. Large field sizes are not practical because the output of the hectocurie unit becomes prohibitively low at 70 cm. source skin distance (SSD). In addition, the penumbra is enormous at greater source skin distances. Furthermore, the energy dissipated in the penumbra can reach a very high percentage of the energy in the geometric beam.[6,11]

The combination of skin sparing and fast fall-off, which characterized the original teleradium units, has advantages in selected clinical circumstances, such as for irradiation of the lymph nodes of the internal mammary chain and in several head and neck conditions. This combination is not possible with supervoltage therapy. There must be two separate units: one for supervoltage roentgen therapy, and another for short source skin distance (approximately 20 cm.) teletherapy.

Table 1 shows the distribution by site of the clinical material treated during the first five years of availability of a kilocurie cobalt 60 unit and a 22 mev. betatron. It illustrates the spectrum of usefulness of supervoltage radiation therapy, ranging from the high dose small volume therapy (as for tumors of the oropharynx or the urinary bladder) to the high dose larger volume therapy for late uterine cervical cancers and to the segmental therapy for lymphomas and ovarian carcinomas. The breast cancers received either preoperative irradiation or irradiation alone. Therefore, the entire chest wall and peripheral lymphatics of the axilla, supraclavicular region,

TABLE I

SUPERVOLTAGE RADIATION THERAPY

February, 1954–May 31, 1959

Site or Type of Tumor	Number of Patients Treated			
	Co^{60}	22 mev. Betatron	Combination*	Total
Cervix	51	717	19	787
Miscellaneous Gynecologic (ovary, body of uterus, vagina, others)	48	71	18	137
Urinary Bladder	47	189	9	245
Testes	22	8	10	40
Miscellaneous Genitourinary (urethra, penis, ureter, prostate, kidney)	10	24	3	37
Head and Neck	658	74	68	800
Breast	208	0	0	208
Lymphoma	102	20	5	127
Thorax (lung, esophagus)	23	43	6	72
Miscellaneous (distant metastases, gastrointestinal, pancreas, others)	73	66	10	149
Total No. of Patients Treated	1,242	1,212	148	2,602

* The patients treated by combination are of two types: (1) cases transferred from one type of therapy to the other due to a change in planning because of new clinical findings or evaluation; and (2) cases in which the 22 mev. betatron was used for localized additional treatment.

upper mediastinum and internal mammary chain were included. The positioning of tangential portals can be time consuming, and a unit allowing a quick, accurate, easily duplicated positioning of tangential portals is desirable.

The third supervoltage unit that was contemplated had to have a beam similar to those of the 2 mev. roentgen-ray generators, a suspension mechanism for maximum speed and accuracy of positioning, large field size for segmental therapy and a collimating device producing minimum penumbra and allowing field shaping. Another 22 mev. betatron was therefore not contemplated, as one was considered adequate for those cases in which treatment with it was indicated. The 2 mev. roentgen-ray generators, because of beam sharpness, depth dose, large field size and high output

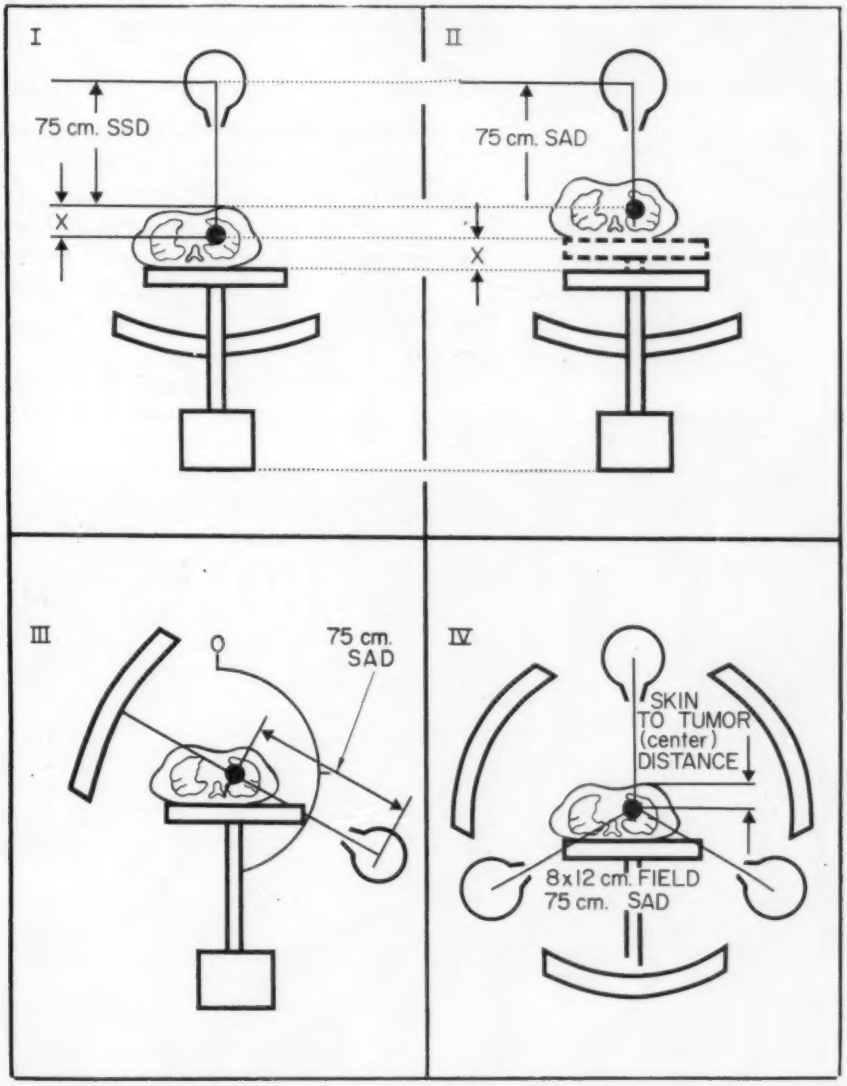

Fig. 1. Drawings showing the successive steps for multiple angulated portal therapy, or rotation therapy. The patient is always in the same position. The surface projection of the tumor and the depth of the center of the tumor are the only necessary data. The tumor is kept at a fixed distance from the target. Tumor-air ratios are used in dose calculation.

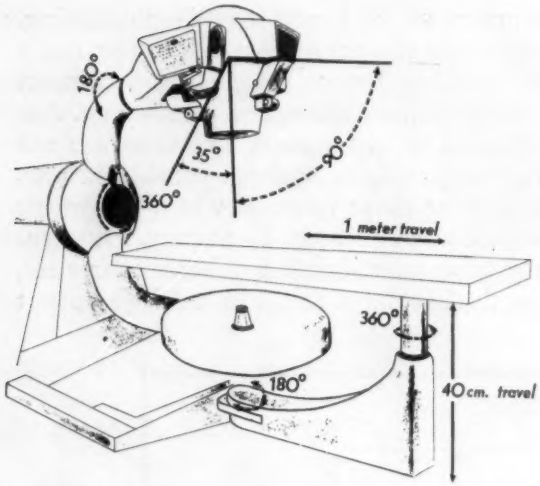

FIG. 2. Drawing showing degrees of motion of the unit.

would fulfill requirements optimally if they were available with a gantry type mechanism. The foreign 4 mev. linear accelerators would have been considered if they had been economically available and serviceable in this country.

Primarily because of space limitation but also because of the desirability of a gantry or a rotational suspension type mechanism, a second kilocurie cobalt 60 teletherapy unit with the following characteristics was acquired: (1) a high activity source of 3,000 curies, rendering 70 cm. SSD economically practical for usual treatments but with 100 cm. SSD still practical for large field therapy, because the daily dose then would be lower; (2) a suspension mechanism allowing stationary portals or rotation therapy; and (3) minimal penumbra and field shaping.

FEATURES OF THE UNIT

Suspension mechanism. A rotation suspension mechanism is superior to a rotating chair for rotating therapy.[1] It is also superior in stationary portal therapy when angulated portals are used because of accuracy, ease and speed of positioning for daily treatments. The gantry mechanism of the 4 mev. linear accelerators had been designed for that purpose. The position of the patient can be the same every day,

FIG. 3. Shaping and double tilting (medial and upward) of an anterior nasopharyngeal portal, using either (*A*) an expanded metal tray with lead blocks or (*B*) an auxiliary diaphragm.

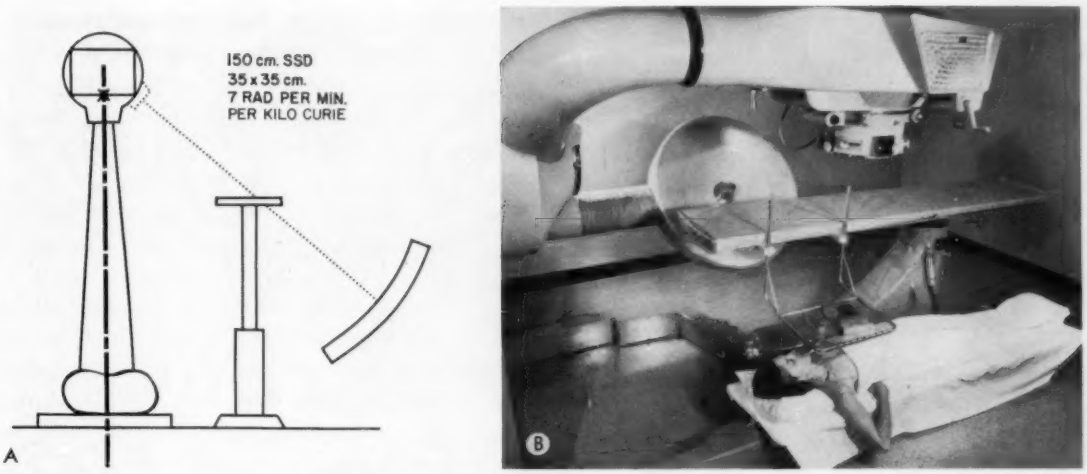

Fig. 4. (*A* and *B*) Segmental therapy requires portals of 35 cm., which is the average length from the pelvic floor to the diaphragm. Daily doses of 100 to 150 r are still economic at 150 cm. SSD with a 3,000 curie source. Less extensive segmental therapy (half abdomen, or mediastinum, or neck and mediastinum) requires portals of approximately 20 to 25 cm. and the SSD can be shortened.

either prone or supine, thus ensuring better anatomic coverage (Fig. 1). For instance, simple parallel opposed portals cannot be used for the upper mediastinum if the patient must be alternately prone and supine. The change of position of the urinary bladder between the prone and supine position is significant. The position-

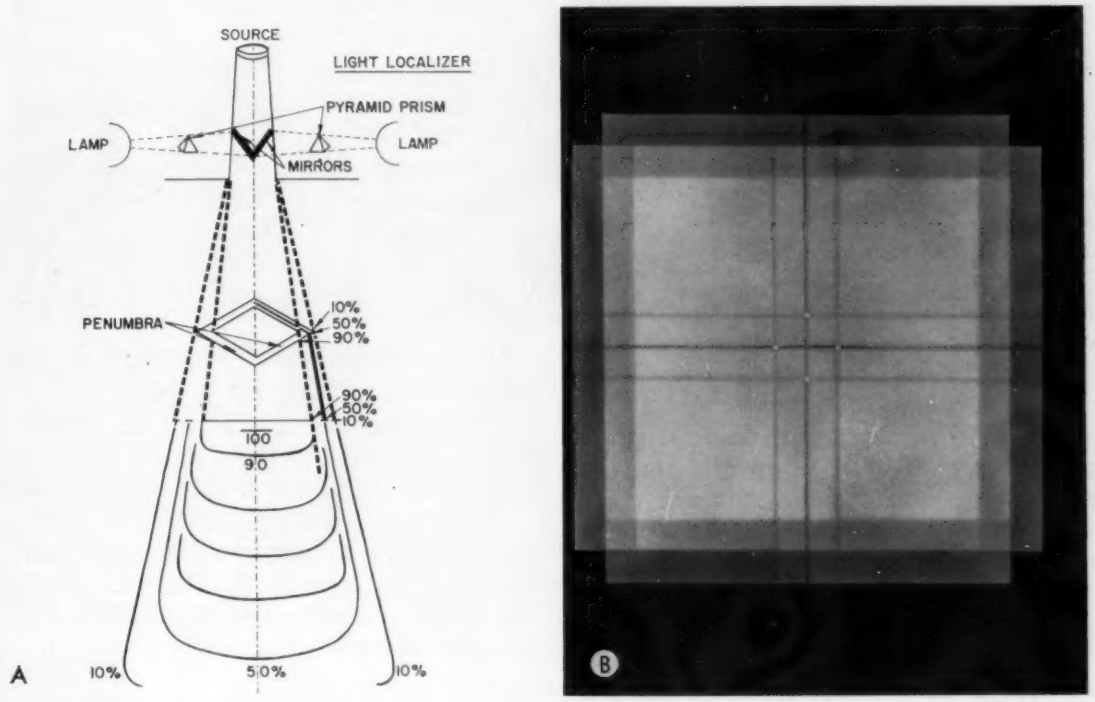

Fig. 5. (*A* and *B*) Two pyramid prisms in the light device superimpose the penumbra of light over the penumbra of rays. The 10, 50 and 90 per cent curves are easily identified on the penumbra of light by the outer, middle and inner lines, respectively.

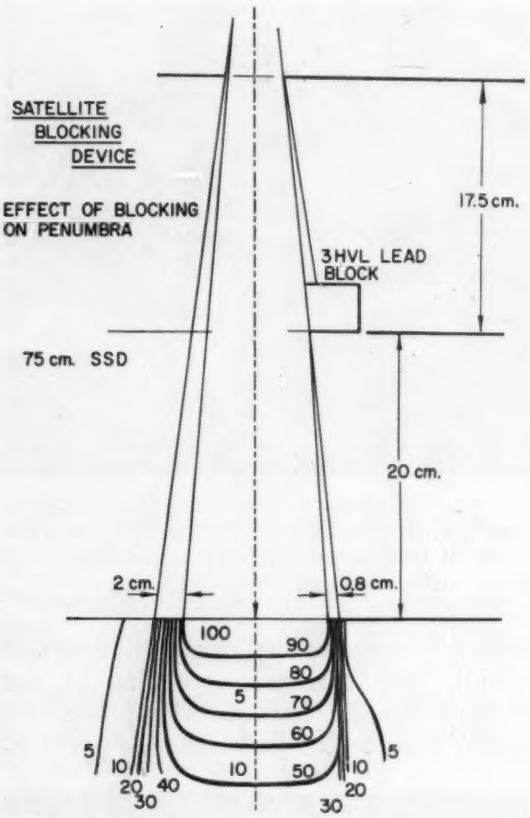

FIG. 6. With an SSD of 75 cm., an auxiliary diaphragm at 20 cm. from the skin reduces the penumbra considerably.

ing of the tangential portals in breast cancer is considerably more accurate and is faster (Fig. 8, *A–F*).

Degrees of motion. In addition to the rotation of the unit and the vertical motion of the table, two other degrees of motion are needed (Fig. 2) because in a number of situations a double tilt is required (Fig. 3, *A* and *B*). Patients can be so dyspneic that they cannot lie down and must be treated in a sitting position. Some therapists prefer to treat head and neck tumors with the patient seated. A side couch can be used for large field therapy (Fig. 4, *A* and *B*).

Collimating device. A light localizer makes a variety of field sizes and shapes available.[2] The primary diaphragm must be placed fairly close to the source in order to have large portals and clearance for rotation therapy. This relatively short distance from the source to the end of the diaphragm produces a significant penumbra.[1] A prism can be placed in the light system to visualize the penumbra (Fig. 5, *A* and *B*).[5]

Auxiliary diaphragms. Secondary electron contamination from the auxiliary diaphragm must be eliminated to avoid skin reactions. With an expanded metal tray, a minimum distance of 10 cm. from the skin is adequate; with a plastic tray, it must be at least 15 cm.[7,9,10] This distance reduces the penumbra satisfactorily (Fig. 6). Auxiliary diaphragms influence output and maximum dose about 3 per cent, which is small enough to be ignored.

It was found that the most satisfactory auxiliary diaphragm for the first cobalt 60 unit was an expanded metal tray on which blocks of either tungsten or lead are placed.[3] The tray can be placed either at the head or along the side of the table (Fig. 7, *A–D*). When angulation of the beam is more than 20 to 25 degrees to the vertical, a rigid diaphragm must be used.

For the tangential breast portals, in order to minimize both the penumbra and divergence of the beam, a special collimator has been built (Fig. 8, *A–F*).

Other accessories. Special head rests are useful for accurate lateral or anteroposterior positioning of the head. A plastic tray and a lateral film holder are available for taking verification radiographs (Fig. 9, *A* and *B*).

Wedge filters can be attached to the collimating device (Fig. 10, *A–F*).

Calibration tables. There are several factors determining the dose at depth of maximum electronic build-up, which is routinely used as the given dose.[8] Calibration charts for cobalt 60 teletherapy units are, therefore, unwieldy. This has led to the design of a calculator which takes into consideration all factors (see Appendix).

SUMMARY

The characteristics and areas of clinical usefulness of supervoltage roentgen therapy

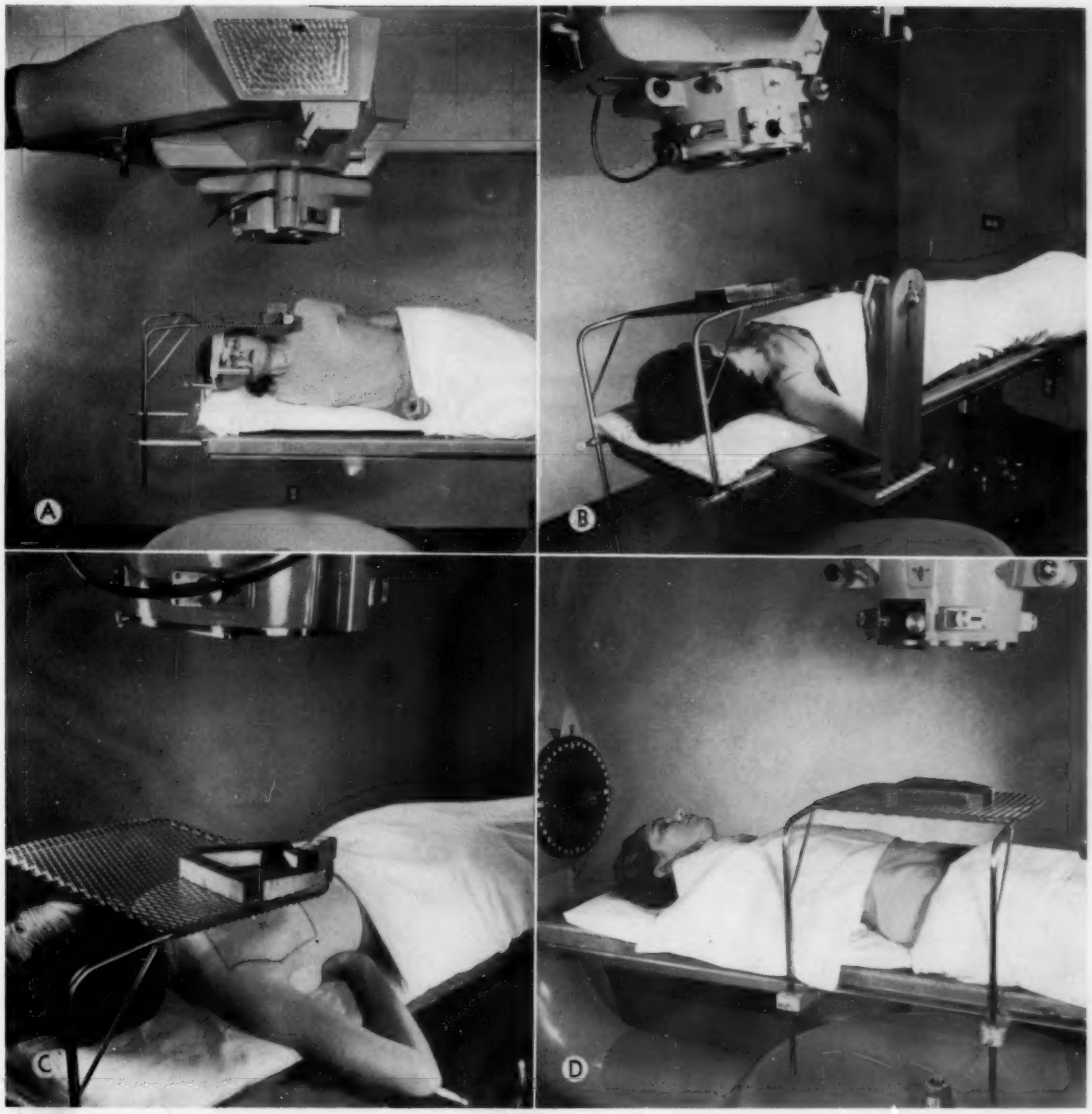

Fig. 7. Examples of field shaping, with lead blocks on an expanded metal tray, for treatment of (*A*) larynx, (*B*) anterior supraclavicular area and axilla (breast carcinoma), (*C*) posterior axilla (breast carcinoma), (*D*) inguinal and iliac lymph nodes.

have been the guide in the design of a second cobalt 60 unit.

Gilbert H. Fletcher, M.D.
Department of Radiotherapy
M. D. Anderson Hospital and Tumor Institute
Texas Medical Center
Houston 25, Texas

We wish to express our appreciation to Atomic Energy of Canada Limited for the design and fabrication of the cobalt equipment, and to E. Dale Trout of General Electric Company, X-Ray Department, for his assistance in preparing the specifications and in the installation of the equipment.

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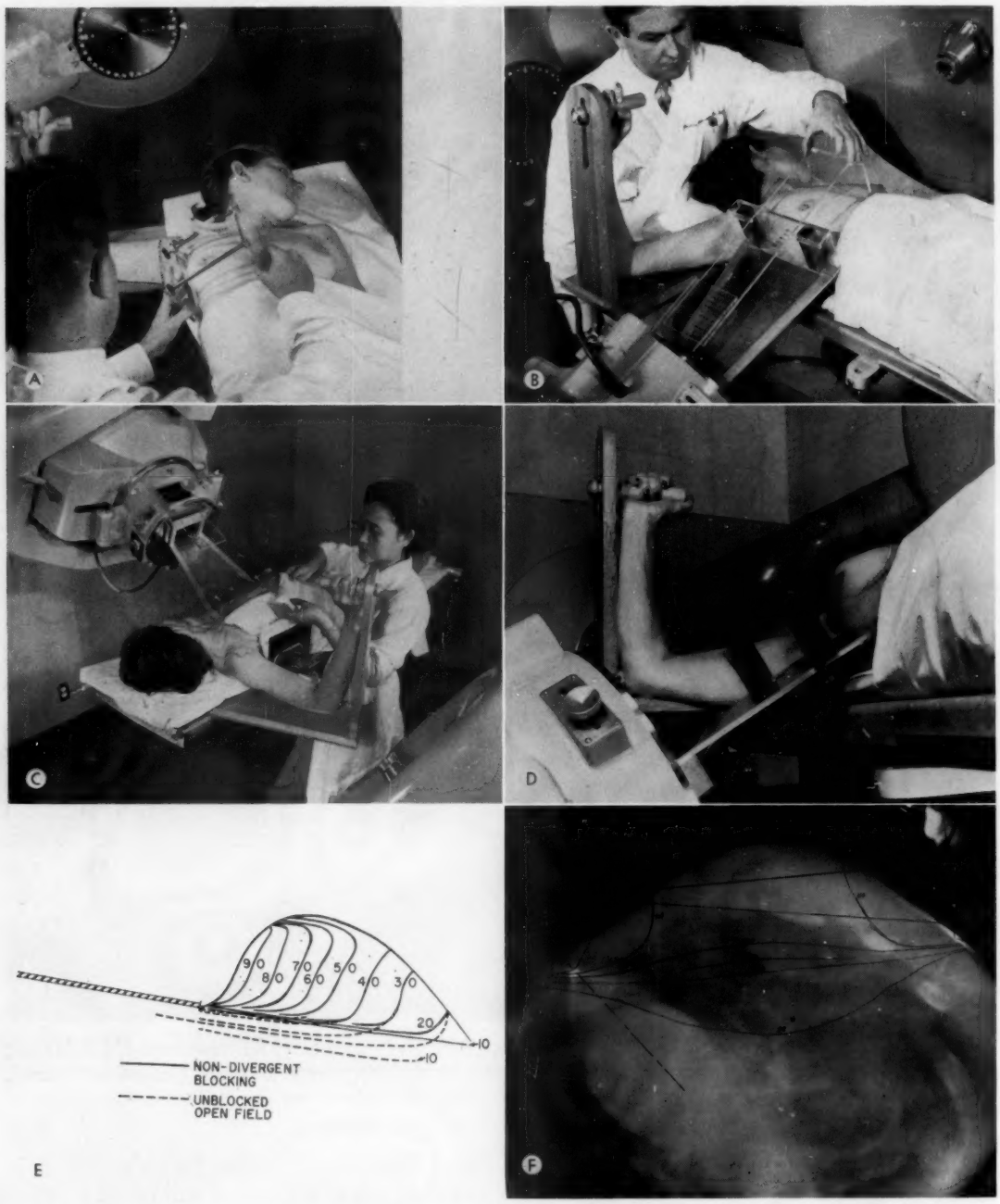

Fig. 8. (*A*) Tangential portals are positioned with the patient supine. The separation of the portals and their angulation is determined with a breast bridge with a spirit level. (*B*) The patient is moved to a collimator which is made of a lead block and a brass plate, taking off from the central axis of the beam and eliminating both penumbra and divergence, as diagrammed in *E*. (*C*) The medial tangential portal with bolus. (*D*) The lateral tangential portal without bolus. Accessory lead blocks delineate the lateral margins of the portal. (*F*) Volume distribution (properly magnified but with no correction for air) superimposed on a transverse laminagram of the patient. The midline of the sternum and the entrance line of the lateral tangential portal were identified with a lead marker. The medial tangential portal is 1 cm. away from the midsternum line and tilted 10 degrees to include the lymph nodes of the internal mammary chain (between 100 to 110 per cent isodose curves—black line).

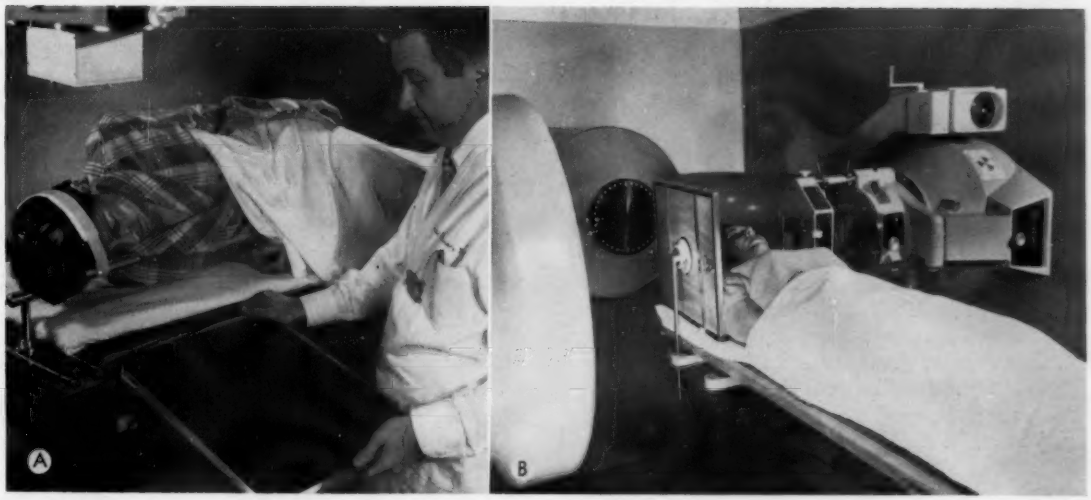

FIG. 9. (*A* and *B*) Illustrations of cassette holders for verification radiographs.

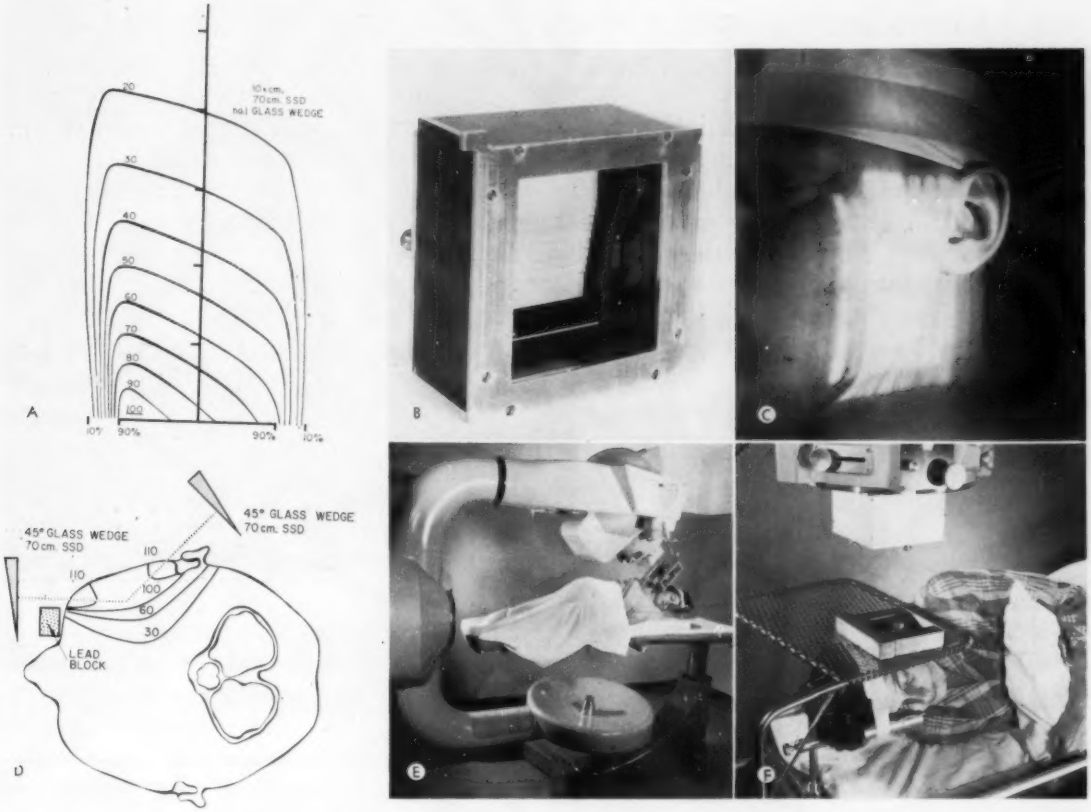

FIG. 10. (*A*) The slope of the isodose curves is sufficiently constant to use the same wedge filter for varying widths. (*B* and *C*) A wedge filter made of plate glass can be used with the light localizer. (*D*) Example of a volume distribution. (*E*) A parotid field and (*F*) a paranasal sinus field, with the eye shielded.

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APPENDIX

A DOSE-TIME CALCULATOR FOR ROENTGEN- AND GAMMA-RAY BEAMS

By EARNEST J. BRAUN, M.D., EARL VAN ROOSENBEEK, *and* R. J. SHALEK, PhD.

THE final variable in radiation treatment by an external beam is the length of time that the patient will be exposed to the radiation. If a number of treatment situations are employed, the compilation of treatment times required for various doses can give rise to a complicated table. With a source of decaying activity, such as cobalt 60, the production of time tables is an onerous task which is subject to the possibility of arithmetic and clerical errors. A simple dose-time calculator for roentgen- and gamma-ray beams, based upon the principle of the circular slide rule, is presented here. With this calculator, the times required for any dose in any treat-

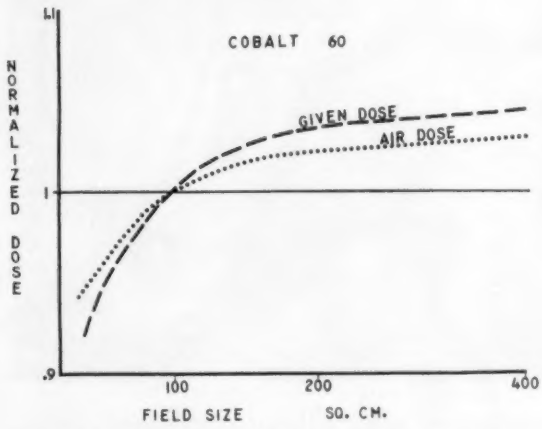

Fig. 1. Comparison of air dose and given dose, curves normalized to 100 sq. cm. field. The given dose is the air dose plus scatter. The air dose change is larger than the change due to scatter alone.

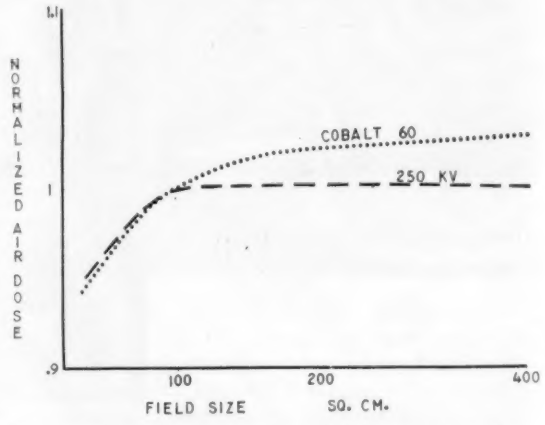

Fig. 2. Comparison of 250 kv. air dose and cobalt 60 air dose. Variations are due to changing field size. The small angle scatter from the total collimating mechanism is the largest factor in determining the cobalt 60 curve.

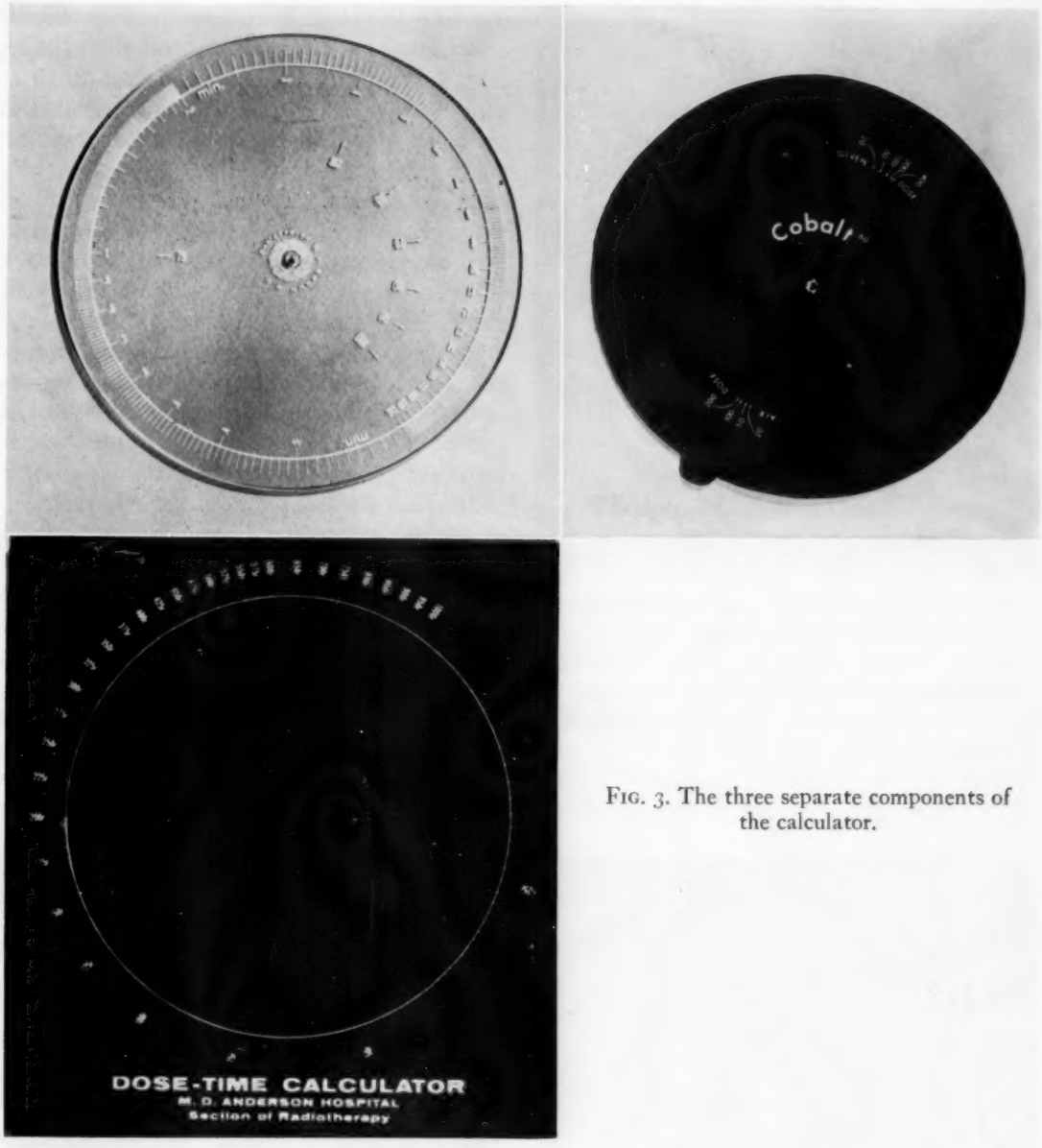

FIG. 3. The three separate components of the calculator.

ment situation are easily determined and, when the dose output of the radiation unit changes, a corresponding change is set on the calculator.

In the construction of a calculator, various factors must be considered. For treatment specifications in terms of given dose it is necessary to include the variation of air dose (due to scatter from collimating parts) and of backscatter factor with field size, and to consider the effect of various target skin distances. With cobalt 60 radiation, the air dose is defined as the dose measured in air at the nominal distance plus 0.5 cm. with an ionization chamber that has sufficient wall thickness. The given dose is the air dose multiplied by the backscatter factor, yielding the dose in tissue at the maximum of the electron build-up curve, which occurs at the nominal target skin distance plus 0.5 cm. In Figure 1 is shown the variation of air dose and of

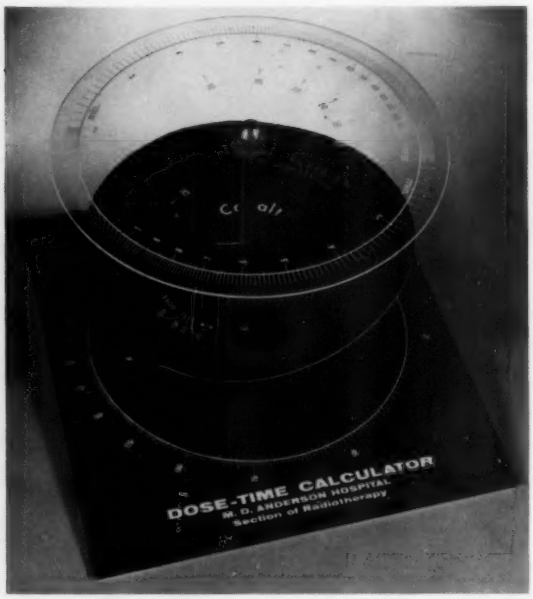

FIG. 4. An exploded view to show relationships of the various components of the calculator.

given dose with field size for a cobalt 60 beam from an AECL Theratron unit. The air dose variation with field size of the unit is compared with 250 kv. air dose in Figure 2. In both cases the curves are normalized to a 10 by 10 cm. field. For roentgen-ray machines the change in output with different filters is a constant factor, and for rotation therapy the air dose at the center of rotation can be included easily in the plan of the calculator.

The calculator consists of an upper transparent disk, a thin opaque middle disk, and an opaque base, as shown in Figure 3. The three parts are held in close approximation by a central axle about which the upper and middle disks can rotate. In Figure 4 an exploded view shows the relationship of the upper and middle disks to the base. The outer scale of the upper disk is in units of minutes on a two cycle logarithmic scale from 0.2 to 20 minutes. Indices for various treatment distances, from 50 to 100 cm., as determined from measurements, are on an inner circle. On the opposite side, the index for 75 cm. air dose for rotation therapy appears; or, in the case of roentgen rays, the indices for different filters are in the appropriate positions. The middle disk has indices on the inner circle for field size; one set of indices is for given dose and another set is for rotational air

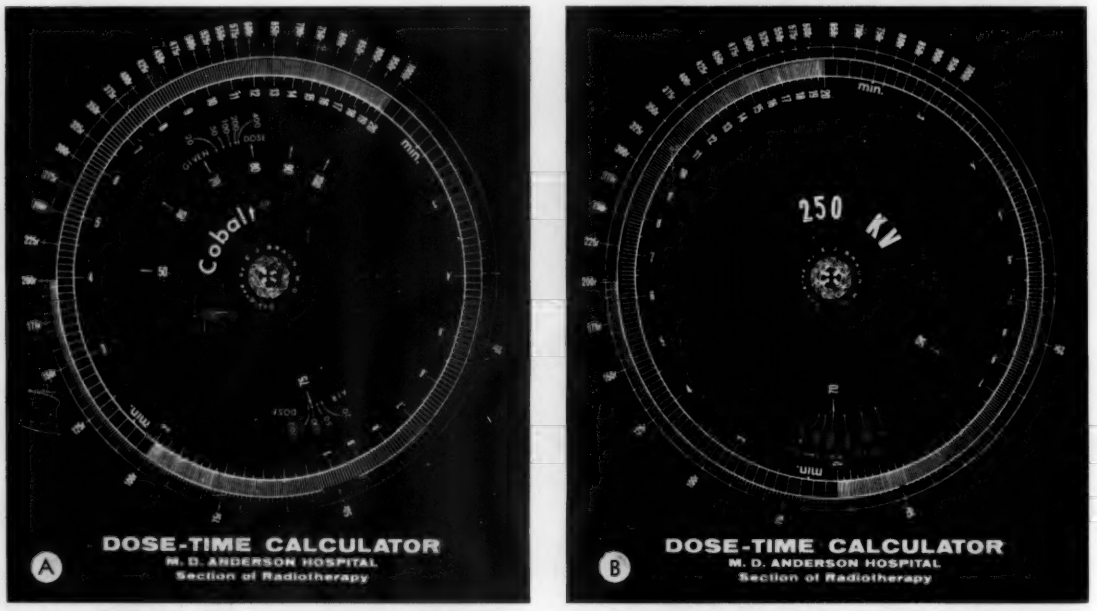

FIG. 5. (*A*) Cobalt 60 calculator set for air dose at center of rotation with a 100 sq. cm. field. The calculator is calibrated for 50 r per hour. (*B*) 250 kv. calculator set for 70 cm. target skin distance, 3 mm. Cu half value layer, 100 sq. cm. field.

dose specifications. On the periphery of the middle disk is an arrow index for setting the output calibration of the radiation unit. The two cycle logarithmic scale on the base has a range of 10 to 1,000 r (or rad). To use the calculator, the middle disk is secured to the base with the index arrow on the periphery at the correct dose rate for a 10 by 10 cm. field, 75 cm. target distance. The index of the desired target skin distance is set on the field size index on the inner circle; the time required is then read opposite the prescribed dose on the outer scales. For example, if the output of the cobalt 60 unit is 47.0 r/min. at 75.5 cm. with a 10 by 10 cm. field, and if a treatment is to be 275 rad given dose with a 12 by 12 cm. field at 70 cm. target skin distance, the procedure is as follows: (1) since, for cobalt 60, 1 rad (muscle) is equal to 0.97 r, the outer index on the middle disk is set at $47.0 \times 0.97 = 45.5$ rad, and the middle disk is secured to the base; (2) the index, 70 cm. target skin distance, is set at 144 cm.^{2} given dose; and (3) on the outer scale, the treatment time of 4.82 minutes is read opposite 275 rad. Figure 5 shows settings for specific factors on a cobalt 60 and a 250 kv. calculator.

In the six months that the calculators have been utilized (for six roentgen-ray machines and two cobalt 60 teletherapy units), the nurse-technicians, who have had little previous mathematical training, have encountered no difficulty in the use of the calculators. The relative physical measurements on the two different types of teletherapy units were similar so that the positions of the indexing arrows were the same on the calculators for both machines; also, a single calculator was found to be valid for two different types of 250 kv. roentgen-ray machines. Before a calculator is applied to a new machine, however, it is necessary to question whether the variation of dose with field size and with distance is the same on the machine as that planned on the calculator.

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Forty-third Annual Meeting: Broadmoor Hotel, Colorado Springs, Colo., May 11–14, 1961.

* *Ex officio.*

EDITORIALS

RADIATION THERAPY AND ADJUNCTIVE CHEMOTHERAPY IN THE TREATMENT OF LYMPHOMAS

THE group of diseases including Hodgkin's disease, lymphosarcoma, reticulum cell sarcoma, and giant follicular lymphoma, collectively referred to as the lymphomas, is best treated by radiation therapy. Despite the primary place of radiation therapy in the management of these conditions, adjunctive chemotherapy has much to offer in certain phases, and particularly in the complicated cases. Of this group, Hodgkin's disease responds best to various chemotherapeutic agents. Reports have also been published as to the efficacy of chemotherapeutic substances in the treatment of lymphosarcoma, reticulum cell sarcoma and giant follicular lymphoma.

Ten of twenty-five sessions at a recent meeting of the American Association for Cancer Research were devoted to the subject of chemotherapy, thus reflecting the great investigative interest in this form of treatment, not only in its application to the lymphomas but also as it concerns cancer in general.

The evaluation of therapeutic methods and improvement in survival rates for the lymphomas differs somewhat from that for other malignant conditions. The tumor host relationship may be different in the patient with a lymphoma than in the patient with a localized carcinoma, since the disease is thought by most to be multicentric at the outset. That the organism limits the extent of therapy, rather than that the tumor is the limiting factor, is well known. Insidious in onset and difficult to recognize in its visceral manifestations, the early diagnosis of these lesions bears a lesser relationship to therapeutic achievement than it does with lesions in more accessible locations and of obvious unicentric origin. Periodic reexamination of the relative efficacy of different methods of treatment is necessary to avoid confusion due to premature conclusions arising from excessive zeal in the interpretation of treatment results.

It is of considerable importance that the various entities within this group of diseases be evaluated individually as to the indications for treatment and the interpretation of results. Thus, it is well recognized that the giant follicular lymphomas, lymphosarcomas and reticulum cell sarcomas are of increasing virulence in the order named.

Surgery as a method of treatment for the lymphomas has been advocated in Stage I lesions, wherein complete excision is attempted. Currently, however, biopsy for the purpose of establishing a diagnosis is the usual limit of the surgical intervention.

Despite general agreement as to the place of radiation therapy in the management of lymphomas, there is considerable variation in its technical application. A vigorous approach wherein tumoricidal doses of radiation are delivered to localized areas, with or without regional or more generalized irradiation, is advocated by some. If, however, the therapist subscribes to the theory of a multicentric origin of such a disease, a more encompassing type of treatment plan may be initiated in the hope that some unrecognized disseminated processes will be treated earlier than would otherwise occur. Localized, intensive therapy is, therefore, more logical in the management of giant follicular lymphoma but is less likely to be employed in the treatment of lymphosarcoma and reticulum cell sar-

coma. The intermediate Hodgkin's disease is usually managed along either of these lines, depending on its clinical manifestations.

The indications for the adjunctive use of chemotherapeutic agents have been standardized in part. Gellhorn[1] and his associates advocate localized aggressive radiation therapy in the patient with an early stage of disease. The patient with multiple sites of involvement receives no irradiation if he is asymptomatic despite evidence of disseminated disease. This approach is based upon the undesirable side-effects from irradiation to multiple sites of the body. Treatment with nitrogen mustard or chlorambucil is recommended in the patient who is symptomatic.

In addition to the original nitrogen mustard compound, methylbis beta chlorethylamine (HN_2), triethylene melamine (TEM) and numerous other chemical substances have been employed in this group of diseases. In general, it may be said that their usefulness is confined to those patients with dissemination, and when used adjunctively to irradiation. Further, this supplementary therapy is most effective in the management of Hodgkin's disease. Lymphosarcoma and reticulum cell sarcoma respond in lesser degree to these agents. Diamond[2] has stated that patients with lymphosarcoma are uniquely sensitive to TEM. The use of chlorambucil (CB 1348) has resulted in no improvement over the results with HN_2 and TEM. This statement applies as well to myleran, actinomycin C and D, and the hemisulfur mustards. He further states that there is no specific antitumor effect of the adrenal cortical steroids on Hodgkin's disease but that such a specific effect does exist in the tissues of lymphosarcoma and reticulum cell sarcoma. In most instances, however, these agents are used in the advanced stages of the disease and where hematologic complications have occurred.

[1] Gellhorn, A., Friend, C., Ultmann, J. E., and Feigelson, P. The lymphomas. *Ann. Int. Med.*, 1960, *52*, 201–222.

[2] Diamond, H. D. The lymphomas. *Disease-A-Month*, January, 1958, 38–60.

The employment of adjunctive chemotherapy or combination therapy with irradiation has proved most effective in the management of disseminated disease with local manifestations of pressure in the mediastinum, on the spinal cord, vena cava, or elsewhere. Campbell and Fromer,[3] in discussing lymphoma cutis, regarding it to be the same as mycosis fungoides, found that all types of chemotherapy are adjunctive to electron beam application. The possibilities of chemotherapy are primarily those of symptomatic relief, questionable resensitization of radioresistant skin, reduction in the amount of electron beam therapy required and the relief of intractable pruritus. It was their observation that steroids, chlorambucil, colcemid and the antimalarial compounds were most effective. They further observed that patients with skin involvement did not benefit from the use of HN_2 or TEM.

More recently Gold and his associates[4] have studied the effectiveness of 5-fluorouracil in the treatment of lymphomas as well as other conditions. They found that toxicity was manifested predominantly in hematologic and gastrointestinal disturbances at all dosage levels of these drugs used and a limited antitumor activity was present. These results were observed despite the use of maximally tolerated doses and they cite the similar experience of other investigators. They conclude that 5-fluorouracil is unlikely to contribute significantly to the therapy of cancer patients.

Miller, Diamond and Craver[5] reported on the use of still another chemotherapeutic substance, epoxypiperazine, an alkylating agent. In treating 48 patients with lymphoma and 12 patients with miscellaneous malignant tumors, significant clinical im-

[3] Campbell, E. W., and Fromer, J. L. Adjunct chemotherapy in treatment of cutaneous malignancies. *S. Clin. North America*, 1959, *39*, 585–590.

[4] Gold, G. L., Hall, T. C., Shnider, B. I., Selawry, O., Colsky, J., Owens, A. H., Jr., Dederick, M. M., Holland, J. F., Brindley, C. O., and Jones, R. A clinical study of 5-fluorouracil. *Cancer Res.*, 1959, *19*, 935–939.

[5] Miller, D. G., Diamond, H. D., and Craver, L. F. The cinical use of epoxypiperazine, new alkylating agent, in treatment of lymphomas and other neoplasms. *Cancer Res.*, 1959, *19*, 1204–1209.

provement was observed in the lymphomas; the type of response, duration of effect and the spectrum of diseases responding were similar to those expected with other alkylating agents.

It thus becomes evident that after ten years of experience with various chemotherapeutic agents, these substances have contributed in some degree to the palliative relief of patients with lymphoma but none of them have contributed to an increased rate of survival. The comparison of patients treated by radiation therapy and chemotherapy is somewhat difficult in that radiation therapy has been employed for approximately forty years as compared to the ten years for the latter. Studies evaluating the chemotherapeutic response of tumors thus are often based on the effect of treatment as determined by regression of tumor masses and other clinical evidences of remission rather than on survival figures. These results must be viewed as less substantive than survival statistics.

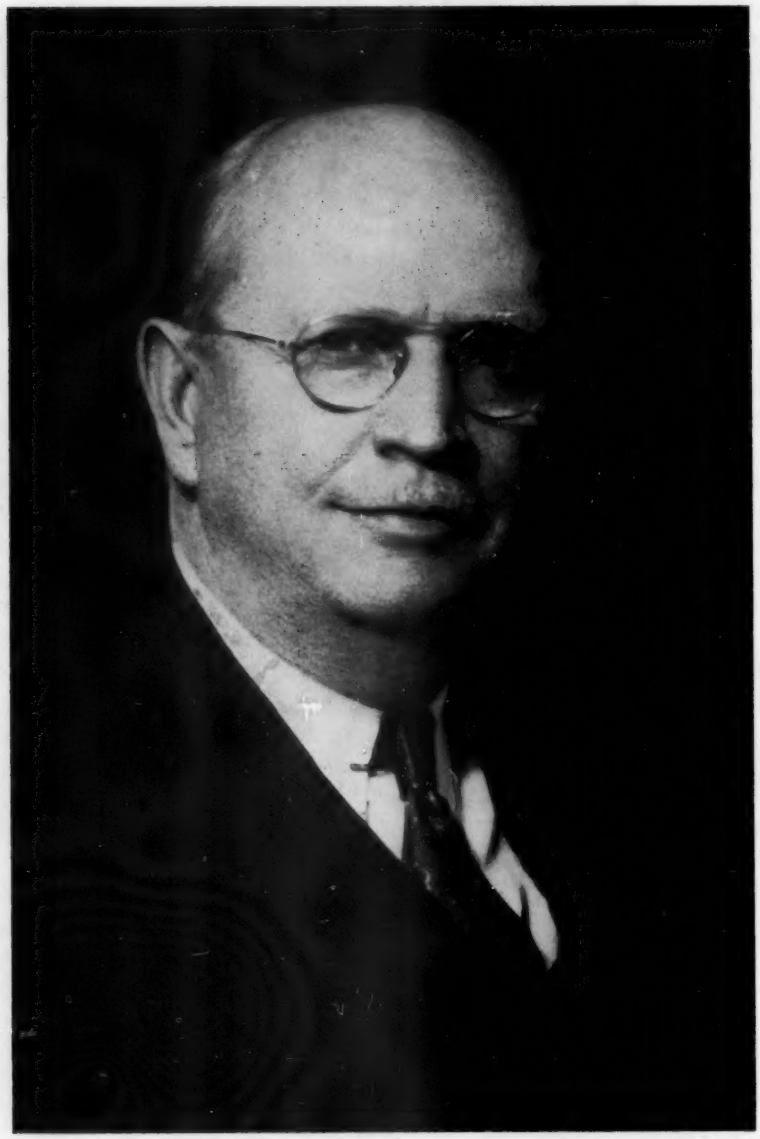
Sugarbaker and Craver[6] twenty years ago indicated the factors influencing the course of lymphosarcoma: (1) its individual inherent qualities for growth and dissemination—probably the most important and the least definable; (2) the extent of the disease when first observed; (3) the location of the primary lesion; (4) whether or not complicating pseudoleukemia or leukemia is present; and (5) the age of the patient. Rather similar observations were made about some of the other members of the lymphoma group.

All in all, it would seem that variations in treatment methods are probably of lesser importance in assessing prognosis than the inherent growth characteristics of the disease. Radiation therapy remains the mainstay of therapeutic methods in the management of the lymphomas. It may be questioned whether prolonged fractionation and large total tumor doses may always be necessary or desirable. Chemotherapy is a valuable adjunct but in our present state of knowledge should not be used as a primary or sole treatment.

Kenneth L. Krabbenhoft, M.D.

Harper Hospital
Detroit 1, Michigan

[6] Sugarbaker, E. D., and Craver, L. F. Lymphosarcoma; study of 196 cases with biopsy. *J.A.M.A.*, 1940, *115*, 112–117.



JAMES THOMAS CASE

1882–1960

An Appreciation

JAMES THOMAS CASE, pioneer and internationally renowned radiologist, died in Santa Barbara, California, on May 4, 1960 at the age of seventy-eight of metastases to the lungs and brain from carcinoma of the ascending colon.

James Case was born in San Antonio, Texas, January 5, 1882, the second of six children. When he was six years old, the family moved to Los Angeles where he obtained his grade and high school education. After finishing grade school he was told that

he could go to high school on condition that he earn his own way. To this end he helped his father construct cement sidewalks in Los Angeles, assisted the janitor of the school building, picked fruit and worked in a cannery.

Mother Case was a Seventh Day Adventist. Although her son later turned away from the strict tenets of that faith, his mother's piety imbued him with a desire to be a medical missionary. In high school, his unusual ability and ambition stimulated him to take additional courses, including Latin and Greek, particularly selected to prepare himself for the study of medicine. He also began the study of Spanish in which he later became exceedingly proficient. One of his teachers suggested that he learn shorthand and typewriting, skills which would be useful later when he worked his way through medical school. He was graduated from high school in 1899, at the age of seventeen, with average grades of 95. This strong desire to learn, manifested in high school, stayed with him throughout his life; in 1956, at the age of seventy-four, he took a course in radioactive isotopes at Columbia University.

After graduation, he was employed for approximately a year as a stenographer by the Pacific Press Publishing Company in Mountain View, California.

About this time, Dr. John H. Kellogg, a Seventh Day Adventist, Administrator and Chief Surgeon of the Battle Creek Sanitarium, Battle Creek, Michigan, through a friend heard of Jimmy Case's plan to study medicine and advised him to go to the American Medical Missionary College in Chicago. At that time, some laboratory subjects were taught in Battle Creek, but anatomic dissections and all clinical work were done in Chicago. In 1910, this institution merged with the University of Illinois.

In August, 1900, when he was eighteen, he went to Battle Creek and tried to register for medical school but was refused because of his youth. He was advised to go back home but, since he did not have the necessary money, he began working in a laboratory as a dishwasher. A little later he was requested to do typing in the receiving office of the sanitarium and to take letters in shorthand for various physicians and patients. During the winter of 1900–1901 he became part-time secretary to Dr. Kellogg.

In the fall of 1901 he was permitted to enter medical school. He tried to continue as part-time secretary to Dr. Kellogg but lost so much sleep that one day he fainted three times in class. After this, Dr. Kellogg refused to use him regularly as secretary and announced that he, Dr. Kellogg, would lend the hard working student the money to go through medical school.

In May, 1902, Dr. Kellogg took Jimmy Case, then twenty years old, to Europe as his secretary. During that summer with his mentor, student Case attended many clinics, heard many lectures and witnessed operations, including the removal of several thyroid glands by the famous Professor Kocher in Switzerland. In Vienna he began the study of German.

After returning from Europe, he registered for the second year in medical school. During the next three student years he accompanied Dr. Kellogg to medical meetings, typed some of his papers and aided in the preparation of manuscripts for his books. He became Dr. Kellogg's surgical assistant. Dr. Case received his medical degree in 1905.

After graduation he still intended to be a medical missionary but the missionary society under which he was to work was in financial difficulty. Dr. Kellogg offered him employment at the Battle Creek Sanitarium. He became the chief surgeon's regular assistant. During this year the chief and his assistant traveled extensively in Northern Mexico under rather rugged conditions and visited a number of medical institutions. In 1909 Dr. Case was appointed to the surgical staff of the Battle Creek Sanitarium and in 1919 was promoted to Surgeon-in-Chief. He continued to perform surgical operations for many years. From 1929 to 1951 he was Consulting Surgeon.

As a medical student he began to work in x-ray diagnosis in 1903. In 1907, he was given full responsibility for the x-ray department at the Battle Creek Sanitarium, which assignment he kept until 1929 when he moved to Chicago.

Dr. Kellogg, who played an important role in Dr. Case's early life, was a strong believer in the value of travel and study in foreign countries. He sent young Dr. Case to Vienna and to Freiburg in 1907, and again in 1911, and to the Curie Institute in Paris in 1912. On one of his trips he went to Russia, where he visited Pavlov's laboratory. He brought back some interesting photographs of these laboratories, in one of which Pavlov himself appears. In 1959 he presented these photographs to the Department of Physiology of the University of California at Los Angeles. During these foreign travels he became familiar with both French and German.

His contributions to medical literature began early in his career. For many years his major interest in diagnostic radiology was the digestive tract. Between 1911 and 1914 he published fourteen papers, two in British and three in German periodicals. He made many original observations; for example, he was the first to demonstrate a Meckel's diverticulum, which was later removed. The biliary tract, the pancreas, roentgenology in obstetrics, as well as miscellaneous topics were objects of his scientific attention. In 1913 he had an exhibit on diverticula of the small intestine at the meeting of the American Medical Association. During these early years his work attracted considerable attention in Europe. Before World War I he was given honorary membership in the Austrian, the German, and the Scandinavian Radiological Societies. About three months before his death, he received a Gold Medal commemorating fifty years of honorary membership in the Société Française d'Électroradiologie.

The first of seven papers on radiation therapy was published in 1915. Throughout his career, he contributed more than one hundred and fifty articles to the medical literature. He edited and participated in the translation from German into English of the large four volume text by Schinz, Baensch, Friedl and Uehlinger entitled "Roentgen Diagnostics," which was published between 1951 and 1954. In 1956, he translated from German the classic text book by Köhler and Zimmer entitled, "The Borderline Between the Normal and the Abnormal in Skeletal Roentgenography." He contributed chapters to many standard text books. In 1914 he published a four volume stereoscopic atlas, "X-Ray Examination of the Digestive Tract."

Dr. Case was either an Honorary or Corresponding Member of innumerable foreign radiologic and other medical organizations, including the Deutsche Röntgengesellschaft, the Royal Society of Medicine and the British Roentgen Society (1917), which was later combined with the British Institute of Radiology, and of many medical societies in the United States. For several years he was Chairman of the Committee on International Affairs of the American College of Radiology.

In later years he traveled extensively and repeatedly in Latin American countries where his fluent Spanish made him a welcome, sympathetic and influential guest. He gave many lectures and held many conferences in Spanish. In 1949 he was made Honorary Professor of the University of San Marcos in Lima, Perú. He was Chairman of the delegation from the United States to the Second, Third and Fourth Inter-American Congresses of Radiology, which were held in Latin American Countries. In 1948, he was given the Orden de Mérito Militar of Mexico.

He was President of the Fifth Inter-American Congress of Radiology in Washington in 1955, during which he was awarded the Gold Medal of the Inter-American College of Radiology, the Orden de Mérito Carlos Finlay by the Government of Cuba, established in honor of the Cuban physician who first suggested that yellow fever was transmitted by a mosquito, and the Orden de Boyacá by the

Government of Colombia. He received honorary memberships in Radiological and Surgical Societies in twelve Latin American countries. Throughout his life he cherished the friendship of innumerable Latin American colleagues and worked constantly to promote international understanding among the nations of the Western Hemisphere. His high standing among his Latin American colleagues was manifested by the gift of a silver tray presented by President Oscar Soto at the Seventh Inter-American Congress of Radiology in Perú in 1958. On this tray is inscribed in Spanish, "James T. Case. Ambassador for Radiology in America." It is now displayed in the Department of Radiology of the University of California at Los Angeles, along with photographs and other mementos from the files of the James T. Case Foundation, which is further described below.

The June, 1960, issue of *Radiología*, the official organ of the Radiological Society of Panama, is dedicated to Dr. Case. It includes warm tributes by Dr. Luis Arrieta-Sánchez of Panama, by Dr. Roberto Calderón of Nicaragua, by Dr. Carlos Coqui of Mexico and by Dr. Frederico García-Capurro of Uruguay. It also contains an obituary prepared at the request of Latin American colleagues by Dr. Juan A. del Regato of Colorado Springs. In this issue it is suggested that steps be taken to erect a bust of Dr. Case in the Garden of the Pan American Union in Washington, D. C.

In 1910 he joined the American Roentgen Ray Society and was its President in 1920. During his term as President, he established the Caldwell lectureship in honor of Eugene W. Caldwell, whom he admired as one of the great early contributors to the advancement of radiology. Dr. Case gave the Caldwell Lecture and received the Caldwell Medal in 1939. He gave the Carman Lecture for the Radiological Society of North America in 1936 and received its Gold Medal in 1950. President of the American College of Radiology in 1929, its Gold Medal was given to him in 1955. He was one of the "Founding Members" of the American Radium Society in 1916, was its President in 1924, gave the Janeway Lecture and received the Janeway Medal in 1959.

In 1916 he was commissioned a First Lieutenant in the Medical Reserve Corps of the U. S. Army. He was sent to France in 1917 as Director of Roentgenology for the American Expeditionary Forces; in this capacity he served until the end of the war. He resigned in 1919 as a Lieutenant Colonel and accepted a commission as Colonel in the Medical Reserve Corps.

During his service in France, he worked with and became the lifelong personal friend of the eminent French radiologist, Antoine Béclère. In February, 1960, he was awarded the Gold Medal of the Centre Antoine Béclère, which was established in Paris after World War II to commemorate the career of this great teacher. For his work in France, he was cited by General Pershing and was given the Purple Heart, then given as a reward for outstanding achievement in the Military Service. Together with Antoine Béclère of France and Robert Knox of Great Britain, he was given an Honorary Diploma in Medical and Radiological Electrology (D.M.R.E.) by Cambridge University in 1921.

In 1916 he succeeded Preston M. Hickey as Editor of the American Journal of Roentgenology. Because of his assignment with the American Expeditionary Forces, he had to resign the editorship in 1918.

He was Professor of Radiology at Northwestern University from 1912 to 1947 and then became Emeritus Professor. In 1959, he received an Award of Merit from the Northwestern University Alumni Association and the Centennial Service Award of Northwestern University Medical School.

From 1929 to 1951, Dr. Case resided in Chicago and, in addition to his academic duties, conducted a private practice. In 1951, he moved to Santa Barbara, California. He became the Director of the Memorial Cancer Foundation and contin-

ued to practice radiation therapy at the Cottage Hospital.

On September 1, 1908, James Case married Helena Kellogg, M.D., daughter of Dr. John H. Kellogg. Mrs. Case had a cerebral accident in May, 1957, which confined her to a hospital bed until her death in August, 1959. During this time Dr. Case cared for her with touching devotion. In August, 1958, their fiftieth wedding anniversary celebration was attended by more than two hundred and fifty friends and colleagues. They received innumerable congratulatory letters, telegrams and cables from all over the world. Dr. and Mrs. Case are survived by a daughter, Mrs. Margaret Cook, Santa Barbara, California, and a son, Mr. Herbert R. Case, Orange, California.

In 1959, the James T. Case Foundation was established by the Department of Radiology of the University of California at Los Angeles. The major objective of this Foundation is to advance the education of residents in radiology at U. C. L. A. by assisting them to attend national radiological society meetings, and to prepare, present and publish reports of investigations in diagnostic and therapeutic radiology. This Foundation was duly incorporated under the laws of the State of California and will stand as a lasting tribute to the achievements of an eminent radiologist.

James Thomas Case was endowed with extraordinary intelligence and with fabulous energy and drive, both intellectual and physical, which did not begin to fade until malignant metastases appeared in the lungs in the autumn of 1959. His work in radiology spanned a period of fifty-seven years. He endured the vicissitudes and disappointments of life with outstanding fortitude. A great radiologist and contributor to medicine has left our scene but his career stands as an example of selfless devotion to his profession and to international human relationships.

Ross Golden, M.D.

IN MEMORIAM

DOCTOR JOSEPH CLARK BELL, born August 10, 1892, died of cardiac failure at the Norton Infirmary April 25, 1960. Doctor Bell was never a man to complain of his affliction and it is doubtful that many, other than a few close friends, knew of the courageous fight he had waged for several years against a failing heart.

Doctor Bell came to Louisville in 1925, at a time when radiology, as a specialty, was hardly out of its swaddling clothes, but was on the brink of new developments and great expansion. With the eagerness, enthusiasm, and indefatigable industry that characterized his entire professional life, Doctor Bell plunged into the work of his chosen field and did much of the pioneering that still stands as a monument to his keen intellect and accurate observation. During this period he published some twenty-five original articles detailing many new techniques and procedures in diagnostic roentgenology.

Doctor Bell practiced a superior type of roentgenology. He left no stone unturned to arrive at a correct diagnosis. His superior qualities were soon recognized at home and abroad and his services were soon in demand, as indicated by memberships and chairmanships in some twenty or more local and national societies. He was President of the Jefferson County Medical Society in 1947–1948, President of the Radiological Society of North America, 1951–1952, and was Chairman of the Board of Directors of that Society in 1949–1950. He held important committee posts in the American Roentgen Ray Society, the American College of Radiology, and many others. He was a founder member of the Kentucky Radiological Society and the Innominate (Medical History) Society.

Doctor Bell was a good teacher. His enthusiasm for learning had a contagious quality that was an inspiration to his listeners. He was always a good and generous friend to all medical students and to the Medical School.

Doctor Bell's professional qualities are nationally well known. Not so widely known, perhaps, were his personal qualities of warm friendship and generous giving of himself that endeared him, not only to his patients, but to a host of friends in Louisville and Kentucky. His passing leaves a void in the professional ranks of Louisville and sadness in the hearts of those many who loved him.

We share our grief with his devoted wife, Lorraine, and all the members of the bereaved family.

Sydney Evans Johnson, M.D.

SOCIETY PROCEEDINGS AND NEWS ITEMS

DR. LAURISTON S. TAYLOR RECEIVES HONORARY DOCTORATE OF SCIENCE

Dr. Lauriston S. Taylor, consultant of the Editorial Board of the American Journal of Roentgenology, Radium Therapy and Nuclear Medicine, was awarded an honorary Doctorate of Science on June 15, 1960 by the University of Pennsylvania with the following citation:

"Your education in physics has led you simultaneously into several broad, yet specialized fields, to all of which you have made signal contributions.

"In the investigation of the measurement of radiation dose, you have been a pioneer, and your leadership has brought about standardization of measurement processes at the international level. As a senior officer in the National Bureau of Standards, you have been concerned with the problems of radiation safety, and you have been instrumental in presenting accurate information to the citizenry and in assisting the various states to formulate protective legislation.

"During the last war your original ideas in behalf of the United States Air Force in England proved to be a vital factor in the early development of operations research."

RADIOLOGÍA HONORS THE MEMORY OF DR. JAMES T. CASE

Radiología, the official organ of the Sociedad Radiológica Panameña, devoted the June 1960 issue to honoring the memory of Dr. James T. Case. Its distinguished editor, Dr. L. Arrieta Sánchez, in announcing the irreparable loss of Dr. Case, "Scientific Ambassador of the United States," writes in a heartfelt editorial, "World Radiology loses one of its foremost surviving pioneers of the present century who, starting their work with the Crookes tube without any protection, have established the high standards which have made the X-rays the most valuable ally of Medical Science."

Dr. F. García Capurro of Uruguay, Dr. Roberto Calderón of Nicaragua, and Dr. Carlos Coqui of Mexico pay warmest tributes to the memory of Dr. Case, not only in the name of their own respective countries but also in the name of all South American colleagues.

Dr. J. A. del Regato of Colorado Springs, Colorado, who is the Counselor for the United States to the Inter-American College of Radiology, contributes the formal obituary in the Spanish language. He concludes his beautiful eulogy of Dr. Case by extoling him "as a man, as a master, and as a friend" who will never be forgotten.

To perpetuate the memory of Dr. Case for future generations, *Radiología* proposes to the authorities of the Inter-American College of Radiology that steps be taken to establish a committee of three, representing the three sections of the Americas: Canada and the United States of North America; Mexico, Central America and Panama; and South America, with the purpose of erecting a bronze or marble bust of Dr. Case in the garden of the Pan-American Union in Washington, D. C.

DR. OTTO GLASSER HONORED

Dr. Otto Glasser, Cleveland, Ohio, was recently awarded the Commander's Cross of the Order of Merit of the Federal Republic of Germany, in recognition of his work on the life of W. C. Röntgen, and his contributions to radiology. Dr. Glasser is also holder of the Röntgen-Honor-Plaque and Honorary Curator of the Röntgen-Museum in Remscheid-Lennep.

NATIONAL RESEARCH COUNCIL OF THE NATIONAL ACADEMY OF SCIENCES ANNOUNCES PICKER AWARDS

On behalf of the James Picker Foundation, the National Academy of Sciences—National Research Council announces the

award of eighteen Research Grants, four Fellowships, and three Grants for Scholars in Radiological Research for the coming academic year. These awards, totaling approximately $121,000, were recently approved by the Foundation on recommendation of the Committee on Radiology of the Academy-Research Council. At the same time, the National Research Council of Canada announces on behalf of the Foundation the award of one Research Grant and one Fellowship for the coming academic year. Including the awards for the coming year, research grants have been made through the United States Academy-Research Council for support of fifty-eight investigations over the ten-year period. These studies were conducted in forty-six institutions throughout the world.

UNIVERSITY OF MINNESOTA CONTINUATION COURSE IN RADIATION THERAPY FOR RADIOLOGISTS

The University of Minnesota announces a continuation course in Radiation Therapy for Radiologists which will be held on the University campus from October 31 to November 4, 1960. Guest participants will include Drs. Jean Bouchard, George W. Casarett, Charles Heidelberger, Morton M. Kligerman, Manuel Lederman, Charles L. Martin, and Philip Rubin. This course is designed for general radiologists who have an interest in malignant disease and its management. An effort will be made to provide a sound basic background for the therapeutic approach as well as practical information on techniques employed in various radiotherapy practices. The course will be presented under the direction of Drs. Harold O. Peterson, Professor and Head, Department of Radiology, and Donn G. Mosser, Professor of Radiology and Director of Radiation Therapy. Lodging and meal accommodations are available through the Center for Continuation Study. Please write to the Department of Continuation Medical Education, 1342 Mayo Memorial, Minneapolis 14, Minnesota.

FIRST INTERNATIONAL CONGRESS ON MEDICAL PHOTOGRAPHY AND CINEMATOGRAPHY

The First International Congress on Medical Photography and Cinematography took place in Düsseldorf from September 27–30, 1960, under the presidency of Prof. Dr. H. Schober, Director of the Institute for Medical Optics in Munich. A free visit to the "Photokina" in Cologne was planned for all Congress members.

FOURTH W. EDWARD CHAMBERLAIN LECTURE

The fourth lecture correlating physiology and radiology honoring Dr. W. Edward Chamberlain was given this year by S. R. M. Reynolds, Professor of Anatomy, University of Illinois College of Medicine in the Temple University Medical School Auditorium at 4 P.M. on Wednesday, September 28. The topic was "Nature of the Fetal Circulation and the Changes at Birth as Revealed Primarily by Cineradiography."

BOOK REVIEW

Books sent for review are acknowledged under: Books Received. This must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interest of our readers as space permits.

Angiocardiopneumographie Élargie. Méthode D'Opacification Vasculaire Générale Par Voie Veineuse. By P. Viallet, Électroradiologiste des Hôpitaux (Alger); L. Sendra, Chef de Clinique à la Faculté de Médecine d'Alger; L. Chevrot, Ancien Chef de Clinique à la Faculté de Médecine d'Alger; P. Aubry, Chef de Clinique à la Faculté de Médecine d'Alger; and P. Combe, Professeur agrégé à la Faculté de Médecine d'Alger. Paper. Price, 4,400 fr. Pp. 110, with 46 illustrations. Masson et C^ie^, Editeurs, 120 Boulevard Saint-Germain, Paris, France, 1959.

The name of general vascular opacification implies standard angiocardiography by intravenous injection. The merit of this technique lies in its utilization of the left phase of angiocardiography, heretofore a neglected field which opacifies vessels located more distally.

To obtain satisfactory results the authors have set up the following requirements:

1. They insist on the necessity of training a staff of well disciplined radiologists, nurses and technicians.

2. An adequate seriograph is necessary and, even better, a large field seriograph, especially when dealing with simultaneous aortography and arteriography of upper or lower limbs.

3. The choice of opaque material is subjected to a detailed discussion. After many trials of various products, the authors have adopted uroselectan 76 per cent (renografin 76 per cent in America) at a rate of 1 ml. per kg. of body weight.

4. Before injection of the opaque material, an equal amount of saline isotonic serum is poured over it with great caution so that it will float without mixing with the opaque medium, due to its lower density. Thus, the opaque material is injected first, followed by the isotonic serum. The serum displaces the opaque residue in the veins and pushes the contrast fluid ahead, acting exactly like a plunger.

5. Usually a vein in the upper limbs is dissected under local anesthesia. However, it may sometimes be more convenient to cannulate a saphenous or an external jugular vein.

6. A simple manual injector (Sendra type), is recommended, with a vertical plunger and a maximum capacity of 200 ml. Therefore, at every moment during the injection, one can always approximate the degree of vascular resistance. The apparatus is linked to a vein by a nylon or plastic tube and a metallic trocar varying from 2 mm. of internal diameter for infants to 7 mm. for adults.

7. The manual pressure exerted on the syringe is about 3.5 kg. per cm.^{2}, for an average duration of one to three seconds.

8. The time and rate of exposures are determined by the speed of circulation, the experience of the radiologist and the anatomic location of the vessels to be investigated. On an average, the rate of exposure is 1 roentgenogram per second for the study of peripheral vessels, 2 or 3 roentgenograms per second for cerebral vessels, and a faster series for the aorta and all the abdominal and thoracic vessels.

9. The authors use a rotating anode tube with a focus 2 mm. in diameter, 600 ma., 100 kv. and 0.03 to 0.5 second at a focus film distance of 1.20 m., standard screen films, Par-Speed intensifying screens, a fine stationary grid, and field limitation by cones, cylinders or diaphragms.

10. On many occasions, two injections in close succession have been performed without any serious effect on the patient.

In the second part of this monograph, the authors give a summary of the results obtained with this technique. Most of the cases studied were of the nature of congenital cardiopathies or of mitral pathology. The accuracy of the angiocardiograms taken during the opacification of the heart cavities and thoracic vessels is equivalent to those made by more selective angiocardiography done with catheters. Moreover, it has been possible to demonstrate morphologic and functional disorders which seem to be characteristic of mitral stenosis and mitral insufficiency, respectively. The method is equally useful in the study of lung or mediastinal tumors and in the determination of their operability. On many occasions, a full opacification of hepatic veins by reflux has been demon-

strated in cases of right heart hypertension or insufficiency. For study of the abdominal aorta and its branches and for lower limb arteries, the authors acknowledge that the angiograms are not always as accurate and sharp as those obtained by direct aortic or arterial puncture, or by selective catheterization, but they emphasize the advantages and the safety of their procedure and the greater value of their findings regarding circulatory dynamics. Interpretation of cerebral arteriograms and phlebograms, however, is rather difficult on account of the unavoidable dilution of the opaque material and because of the superimposition of the external carotid ramifications and, on lateral films, the addition of symmetric vessels from both cerebral hemispheres. Frequently it seems impossible to detect small aneurysms. Interestingly, the basilar and posterior cerebral arteries are always delineated except when obstructed.

The authors recommend that this type of opacification always be performed as a preliminary screening method, which must sometimes be supplemented by direct carotid or vertebral arteriography, just as intravenous urography should almost always precede, and frequently replace, retrograde pyelography.

The monograph has many illustrations; most of them are taken from angiograms of children which, admittedly, show better vascular contrast than is usually seen in those of adults.

The authors report promising results in nephrography, in placentography and even in splenohepatography, using this general opacifying method.

Paul Roy, M.D.

BOOKS RECEIVED

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ABSTRACTS OF RADIOLOGICAL LITERATURE

Department Editor: T. Leucutia, M.D., Harper Hospital, Detroit 1, Michigan

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ROENTGEN DIAGNOSIS

Head

Pecker, J., Javalet, A., and Stabert, Ch. L'angiographie dans les traumatismes craniens. (Angiography in cases of cranial trauma.) *J. de radiol., d'électrol. et de méd. nucléaire*, Nov., 1959, *40*, 623–638. (From: Clinique neurochirurgicale de Rennes, Rennes, France.)

Several illustrative cases are presented to emphasize the importance of cerebral angiography, which, in the experience of the authors, has been a safe and harmless diagnostic procedure. However, a few limitations and contraindications should be borne in mind. There are times when emergency cranial surgery militates against loss of a precious half hour needed for angiography; in other instances, because of cerebral edema, angiographic detail would be blurred and hence the procedure would be unsatisfactory for diagnostic purposes; also, angiography should perhaps be omitted in hypertensive patients with atheromatous disease.

Anteroposterior and lateral roentgenograms taken at one second intervals will demonstrate arterial, capillary and venous return phases of cerebral circulation. In certain cases where bilateral opacification is desirable, compression of the opposite common carotid will suffice.

Two extradural, 2 subdural and 1 intracerebral hematoma suspected clinically were confirmed by angiography.

In the 2 cases of subdural hematoma (1 of which was bilateral) angiography led to the correction of an erroneous clinical diagnosis and localization. However, in another case where bilateral subdural hematoma was diagnosed because of the lack of shift of the anterior cerebral and pericallosal arteries, it was discovered at surgery that this was due to a partial collapse of the cerebral hemisphere, since no bilateral hematoma could be found.

In a case of basal temporal hematoma, angiography pin-pointed the site of the lesion, thereby leading to accurate trepanation.

Angiography is of importance in cases of cranial trauma with protracted, indefinite symptoms. An epileptic patient with a history of many falls over a period of years and suspected of having either a brain tumor or a hematoma (a diagnosis based on hemiplegia and eye findings) was shown by angiography to have a large parietal hematoma. Lateral angiographic views showed lack of visualization of the parietal cerebral vessels, an example of the importance of lateral views. Another patient with long standing post-traumatic symptoms was demonstrated by cerebral angiography to have a right intracerebral (frontal) and a left extradural hematoma.

Finally, angiography is useful in diagnosing and localizing post-traumatic intracranial lesions other than hematomas. A case of thrombosis of the middle cerebral artery and another of the internal carotid artery were clearly diagnosed by angiography and correct treatment was instituted. Cases of temporal lobe atrophy (the middle cerebral artery has a broken line appearance), a brain abscess noted three years after a compound fracture of the skull (angiography shows the same degree of displacement of the vessels as in intracerebral hematoma), and a very large aneurysm of the middle cerebral artery in a young boy are all presented for differential diagnostic purposes as well as to stress the importance of angiography in instituting the right treatment.—*Jirair Sarian, M.D.*

Webster, J. E., Gurdjian, E. S., Lindner, D. W., and Hardy, W. G. Proximal occlusion of the anterior cerebral artery. *A.M.A. Arch. Neurol.*, Jan., 1960, *2*, 19–26. (Address: E. S. Gurdjian, 1553 Woodward Ave., Detroit, Mich.)

Nonfilling or thread-like filling in angiographic studies of the proximal portion of the anterior cerebral artery may be due to occlusive atherosclerosis, or to a congenital abnormality, with a small proximal anterior cerebral artery on one side or the other. Although the incidence of a small proximal anterior cerebral artery on one side in routine autopsies is about 2 per cent, among patients with symptoms and signs of cerebrovascular disease small or nonfilling anterior cerebral arteries were found in 11 per cent.

This type of disturbed cerebral circulation may result in both neurologic and psychiatric disturbances with weakness, anxiety and poor mentation, probably related to hypothalamic derangement. Weakness of the contralateral half of the body, greatest in the upper extremities, was found in one-third of the patients.

The diagnosis is made by angiography supplemented by the carotid artery compression test.—*James J. Mc Cort, M.D.*

Kotscher, E. Familiäres Auftreten von endokraniellen Verkalkungen bei Lipoproteinose. (Familial occurrence of endocranial calcifications in lipoproteinosis.) *Radiologia Austriaca*, 1960, *10*, 299–303. (From: Zentral-Röntgeninstitut der Universität Wien, Vienna, Austria.)

Lipoproteinosis is a very rare skin disease characterized by nodules in the skin and mucous membranes which consist of amorphous masses of lipoids and proteins. Endocranial calcifications have been previously described.

The author's cases, a twenty-seven year old woman and her thirty-five year old brother, were diagnosed as lipoproteinosis by skin biopsy. Roentgen examination of the skull showed, in both cases,

very similar findings. Spindle shaped, dense calcifications were seen above the dorsum sellae; on a frontal projection they were in the medial portion of the orbits.

In 77 cases of lipoproteinosis published to date, 8 showed very similar calcifications. The abnormal calcifications are most likely to be found in the brain substance in the temporal lobe and in the region of the gyrus hippocampi. Autopsy findings are not as yet available.—*H. W. Hefke, M.D.*

Neck and Chest

Katz, Isadore, and Wagner, Stephen. Unilateral pulmonary "emphysema." *Radiology*, Sept., 1959, *73*, 362–366. (Address: I. Katz, 450 Clarkson Avenue, Brooklyn 3, N. Y.)

Unilateral pulmonary emphysema is a condition in which there is increased radiolucency of one lung associated with decreased prominence of its hilar and pulmonary vascular markings. A case report is presented adding to the few that have previously been reported in the literature. This condition, while similar to other forms of airway obstruction, differs from them in that there is absence of major bronchial occlusion demonstrable by bronchography.

Clinically, the onset of symptoms is not noticed by the patient. Mild to severe shortness of breath usually following mild exertion is most often the outstanding complaint. This develops slowly over a period of years and may be aggravated by acute upper respiratory infections. Cough is occasionally present. The entire clinical course is quite benign, the findings often remaining stationary for many years.

Roentgenographically, the characteristic findings are unilaterally decreased prominence of the pulmonary vascular shadows and a corresponding decrease in the size of the hilar shadow as contrasted with that of the opposite lung. In approximately 50 per cent of cases the mediastinum is displaced toward the affected side on inspiration. Expiratory roentgenograms accentuate the radiolucency of the abnormal lung, while the normal side becomes less radiolucent as the mediastinum shifts away from the affected lung, moving either back to the midline from its position on the abnormal side or over into the normal lung field if it was originally in a central position. The diaphragm on the affected side rises only slightly on expiration. In the remaining cases the mediastinum shifts away from the affected side on inspiration. These roentgen findings remain unchanged over a period of years, fifteen years in the case reported here. Bronchography reveals complete patency of the bronchial system of the abnormal lung. No gross intra- or extrabronchial obstructive mechanism is found in the major or segmental bronchi, and their spatial distribution within the lung is normal. Angiocardiography shows hypervascularity of the normal lung and hypovascularity of the abnormal lung. It also rules out the presence of a congenitally absent pulmonary artery.

Physiologic studies reveal decreased function of the abnormal lung in all aspects. Since pathologic studies have been available in only 2 patients, with no consistent findings present, the nature of the basic pathologic process remains unknown. It is theorized that repeated pulmonary infections during infancy or childhood may impair the growth of the lung probably resulting in eventual decreased pulmonary elastic recoil and distensibility.

The differential diagnosis must include the obstructive and compensatory types of emphysema, congenital absence of either the right or left pulmonary artery, and some pulmonary malformation, such as agenesis of a lobe and stenosis of a bronchus. Fluoroscopy, bronchography, and angiocardiography will help in the differentiation.—*Donald N. Dysart, M.D.*

Michelson, Elliott, and Salik, Julian O. The vascular pattern of the lung as seen on routine and tomographic studies. *Radiology*, Oct., 1959, *73*, 511–526. (Address: J. O. Salik, Sinai Hospital of Baltimore, Inc., Baltimore 5, Md.)

Recognition of the normal and abnormal vascular pattern on laminagrams and routine roentgenograms has proved to be of definite value in the interpretation of lung lesions. This study endeavors to present the prevailing normal pulmonary vascular pattern while recognizing that many variations may be found.

The bronchial and vascular anatomy is briefly reviewed, using both the nomenclature recommended by the International Congress of Otorhinolaryngology in London (1949) and Boyden's shorthand numerical system. In the anteroposterior laminagrams of average patients, the greater part of the bronchovascular pattern can be seen at levels from 8 to 12 cm., measuring from the back. The middle lobe and lingular segment are seen at more anterior levels. The bronchi should be visible as far as their segmental branches; only arteries and veins can be seen beyond this point. If the normal architecture is known, it should be possible to determine lesions which modify the position, the arborization or the caliber of the vascular system.

While there is a great deal of variation in the vascular lung pattern, the basic picture is easily recognized and, after a close study of the vascular tree by laminagraphy, it is surprisingly easy to trace a great number of vessels on routine posteroanterior and lateral chest roentgenograms. In the segments proper, the veins course along the periphery, while the artery and bronchus are within the center of the unit. The pulmonary arteries arch downward from the hilus, producing a weeping willow pattern. The pulmonary veins enter the mediastinum below the

arteries and their course to some extent describes a reverse arch to the arteries giving the appearance of a zodiac crab. Since a vein and its corresponding artery cross at right angles somewhere within the middle portion of the lung field, the differentiation can be made by following the course of the vessel back toward the hilus.

Several illustrations are presented, including roentgenograms and a three-page colored line drawing suitable for framing.—*Walter H. Jarvis, Jr., M.D.*

Bell, A. L. Loomis, Jr.; Shimomura, Seiichi; Guthrie, W. James; Hempel, Herbert F.; Fitzpatrick, Hugh F.; and Begg, Charles F. Wedge pulmonary arteriography; its application in congenital and acquired heart disease. *Radiology*, Oct., 1959, *73*, 566–674. (Address: A. L. L. Bell, Jr., St. Luke's Hospital, New York 25, N. Y.)

The authors describe a clinical technique for visualizing roentgenographically the small pulmonary arteries; they outline the preliminary results of this method in 38 patients with congenital or acquired heart disease. During right heart catheterization a catheter is maneuvered into a pulmonary artery and the tip is "wedged" in an area of clear lung field free from mediastinal shadow, scapula, etc. After the wedge position is checked by a pressure measurement, the patient holds his breath in deep inspiration and 2 or 3 cc. of 70 per cent urokon is injected, followed by a saline flush of 5 to 10 cc. An exposure is made at the time of injection. The resultant roentgenogram is enlarged for better definition and the actual intraluminal diameter can be ascertained by a factor derived from the actual diameter of the catheter used.

In preliminary studies, the wedge pulmonary arteriogram correlates well with the histologic picture of the pulmonary vasculature as seen in patients where widespread occurrence of obstructive intimal lesions of larger muscular arteries is the major cause of increased resistance to pulmonary flow. Here, the arteriogram shows sparsity of arborization of the small pulmonary arteries, abrupt termination of arteries 500 to 1,500 μ. in size, and abrupt narrowing of vessels of similar size into fine tortuous channels. This "pruned tree" appearance results from widespread occlusive intimal fibrosis present in arteries of from 300 to 1,200 μ.

The arteriogram in patients with increased pulmonary blood flow and normal pressure shows some slight increase in arborization and capillary filling. This corresponds to the histologic demonstration of dilated and tortuous small vessels seen in lung biopsies of patients who have had atrial septal defects repaired.

Patients having elevated pulmonary artery pressures related to high left atrial pressures from mitral stenosis reveal decreased arborization with sparsity of background markings from decreased arteriolar and capillary filling. No abrupt termination of arteries is noted. This decreased arborization is believed to be due to muscular hypertrophy of arteries with narrowing of the lumen. However, differentiation from the normal could not be made with certainty in many of the group with pulmonary hypertension.

The authors conclude that this technique provides a satisfactory means for differentiating cases in which occlusive, and presumably fixed, changes in the pulmonary vasculature have occurred and for which the surgical correction of the associated cardiac defect is thus contraindicated.—*John S. Alexander, M.D.*

Falkenbach, Karl H., Zheutlin, Norman, Dowdy, Andrew H., and O'Loughlin, Bernard J. Pulmonary hypertension due to pulmonary arterial coarctation. *Radiology*, Oct., 1959, *73*, 575–590. (Address: B. J. O'Loughlin, School of Medicine, University of California, Los Angeles, Calif.)

Partial atresia of the main branches of the pulmonary artery was first reported by Oppenheimer in 1938. Sondergaard (1954) suggested the term coarctation because of the apparent connection between the central constriction of the artery in his case with the closing of the ductus arteriosus (scodiac theory). Altogether, 16 cases of pulmonary artery constrictions have been reported in the world literature. These are reviewed in this paper. To them the authors add 7 of their own cases.

It is the opinion of the authors that none of the previous writers had established a causal relationship between pulmonary arterial coarctation and the development of pulmonary hypertension. The purpose of the present study is to demonstrate that coarctation of the pulmonary artery or one of its main branches is invariably associated with pulmonary hypertension. By ligaturing the main pulmonary artery in four to six week old puppies, and letting them grow up with the silk suture ligature (as children grow up with coarctations of the aorta) the authors demonstrated that experimentally produced pulmonary artery coarctation in fact causes pulmonary hypertension. Their technique is discussed and experimental results are tabulated.

Three types of constrictions have been identified roentgenologically: central (or scodiac), main branch, and peripheral types. Frequently there are associated cardiovascular defects, the most common of which is valvular pulmonic stenosis. Others include septal defects, patent ductus, tetralogy of Fallot and patent foramen ovale.

Brief case reports are presented of the authors' 7 patients and the significant laboratory and clinical data are tabulated. Several characteristic roentgenograms taken during angiocardiographic studies are also presented. The chief clinical findings are as

follows: (a) a harsh systolic murmur is heard at P_2 with P_2 greater than A_2 (P_2 is split if there is associated pulmonic valvular stenosis); (b) the lesion is usually asymptomatic in its early stages, then later becomes manifest by progressive exertional dyspnea; cyanosis and dyspnea in newborn infants is not an uncommon occurrence but such cases usually have associated cardiovascular defects; and (c) no characteristic familial or birth history was evident in these cases.

The chief laboratory findings include: (a) right ventricular hypertrophy both on electrocardiograms and roentgenograms; (b) increased pressure in the lesser circulation found at the time of angiocardiographic studies, with a "step-up" in pressures occurring as the catheter is withdrawn through each coarcted segment (pressure tracings are presented to show these changes); and (c) oxygen saturation at the lower limits of normal in uncomplicated cases. Where other defects occurred in association with the pulmonary artery coarctation, the characteristic findings were added to those of the arterial constriction.

An extensive discussion as to etiology and exact mechanism of production of the pulmonary hypertension is presented. The most likely explanation is suggested by the work of Goldblatt and of Cournand. Hypoxia or ischemia of the involved lung may stimulate the right ventricle to increase pressure proportionately to the degree of pulmonary artery coarctation, or the ischemic lung may liberate a heretofore unknown substance which has the same effect.

An excellent bibliography is appended of additional related information.—*Z. Petrany.*

Fleischner, Felix G. Unilateral pulmonary embolism with increased compensatory circulation through the unoccluded lung. *Radiology*, Oct., 1959, *73*, 591–597. (Address: Beth Israel Hospital, 330 Brookline Ave., Boston 15, Mass.)

The awareness that nonfatal pulmonary embolism may be recognized by roentgen examination has resulted in a marked increase in the number of cases discovered in some hospitals. The most important and conclusive roentgen contribution to the diagnosis of pulmonary embolism is the recognition of a pulmonary infarct. Less conclusive signs are pleural effusion, inhibited respiration often accompanied by pulmonary edema, and signs of acute and chronic cor pulmonale or pulmonary hypertension, including also the roentgen evidence of the oligemic lung field and the plump hilar shadow.

The author describes additional roentgen signs observed in massive unilateral pulmonary embolism. He presents his observations in 2 patients. The radiolucency of the lung on the side of occlusion is increased. This is due to the oligemic capillary background. The visible individual vessels are narrower and fewer in number. In the unobstructed lung, the hilar and peripheral vessels are wider, owing to the overflow of blood to this side. The hilar shadows may be plump if the embolic obstruction is not located immediately beyond the bifurcation of the pulmonary artery. This may be due to the embolothrombus lodged there or to the pulmonary hypertension associated with the pulmonary embolism.

There are also many interesting physiologic observations. The cardiac output remains unchanged. The velocity of the blood in the pulmonary vessels increases and about twice the usual flow per minute passes through the unoccluded lung. The involved lung remains viable because the nutrient blood supply provided by bronchial circulation is sufficient. The ventilation of this lung remains unchanged; however, there is little gas exchange because the functional (pulmonary) circulation in the affected lung has been excluded. When the large embolus breaks up, dissolves, or when reflex vasospasm subsides, the normal blood flow through the embolized lung may be restored and the overflow to the other side stopped. There is a slow restoration of the vascular tree to normal on the embolized side. However, if the embolism leads to chronic narrowing of the arterial bed on the affected side, the overflow to the unoccluded side and the widening of the vessels there become permanent.

In the differential diagnosis one must consider agenesis and hypoplasia of the pulmonary artery, unilateral obstructive emphysema with or without bronchial obstruction, unilateral restrictive emphysema (*e.g.*, after pleurisy), mediastinal or hilar primary or metastatic carcinomatous masses constricting or invading the pulmonary artery, and the idiopathic unilateral hyperlucent lung.—*W. M. McBride, M.D.*

Kis-Várday, Gyula. Aortenkalzifikationen im Kindesalter. (Calcifications of the aorta in childhood.) *Fortschr. a. d. Geb. d. Röntgenstrahlen u. d. Nuklearmedizin*, Feb., 1960, *92*, 134–138. (Address: Üllöi út 78/b, Budapest, Hungary.)

About 50 cases of calcification of the aorta in the newborn and children have been described in the world literature. Among the causes, congenital vascular anomalies figure first (partial pulmonary atresia); also included are congenital aortic hypoplasia in, or without connection with, aortic aneurysm, congenital lues, and extensive arteriosclerosis in progeriac children. Other factors such as disturbed lipoid metabolism in diabetes, myxedema, xanthomatosis, as well as acquired atheromatosis in children fed cholesterin-rich diet have been described by Ssolowjew. In many of the reports, the importance of calcium metabolism is stressed in connection with renal insufficiency, hyperparathyroidism, and vitamin D hypervitaminosis.

The author presents 4 cases with calcific deposits

in the ascending aorta and arch: a seven-year old girl with prolonged vitamin D therapy from birth and without definite patholgy; a five-year old boy with vitamin D therapy of few years' duration for chronic rickets (this patient exhibited aortic hypoplasia); a six-year old girl with a fist-sized aneurysm of the ascending aorta with shell-like calcification; and a nine-year old boy operated two years previously for coarctation of the aorta with calcifications having developed at the site of anastomosis.

In the first two cases, the combination of chemical agents with congenital disposition of the connective tissue, especially the hypoplasia in the second case, was probably the contributing factor.—*Nathan Kriss, M.D.*

Mahoney, Paul S., and O'Loughlin, Bernard J. Significance of calcification of the wall of the left atrium; report of two cases. *Radiology*, Sept., 1959, *73*, 402–405. (Address: B. J. O'Loughlin, University of California Medical Center, Los Angeles 24, Calif.)

Calcification of the wall of the left atrium is a complication of long standing rheumatic heart disease, and the severity of the auricular involvement is related to the severity of the valvular disease. Pathologic changes are chiefly subendocardial plaque formation, fibrosis, connective tissue hyperplasia, and Aschoff's nodule formation. The diagnosis can usually be made on a plain roentgenogram but overexposed film using a Bucky diaphragm, laminagraphic studies, or roentgen cinematography may be needed to confirm the diagnosis.

The differential diagnosis should include other structures in the heart which may calcify; most important and most difficult is the differentiation between a partially calcified mural thrombus and a calcified left atrial wall. Intramural calcification is usually linear, nonlaminated, and marginal in distribution. A calcified mural thrombus is laminated and nonlinear. The identification of calcium in the wall of the left atrium is particularly important in potential valvulectomy cases, since its presence may cause the surgeon to reevaluate the patient.

The authors add 2 cases to the 31 previously reported in the literature.—*James C. Moore, M.D.*

Pecorini, Victorio, Macchi, Roberto J., Suarez, Luis D., and Perosio, Albino M. Persistencia de la vena cava superior izquierda. (Persistence of the left superior vena cava.) *Prensa méd. argent.*, Oct. 2, 1959, *46*, 2409–2416. (From: Hospital de Clinicas, Buenos Aires, Argentina.)

The most satisfactory methods for diagnosis of a persistent left superior vena cava are cardiac catheterization, angiocardiography, and selective angiocardiography. In 200 cases of congenital heart disease in which cardiac explorations were done, 8 cases were found where there was a persistent left superior vena cava. In 7 of these cases, there was also a right superior vena cava. Other anomalies associated with a persistent left vena cava included a shunt of the right and left superior vena cava at the level of the auricles, shunt at the level of the ventricles, anomalous pulmonary vein and tetralogy of Fallot-Corvisart. When the left superior vena cava empties into the right ventricle, surgical treatment is not necessary.

The diagnosis was not made correctly by ordinary clinical methods in any of the 8 cases which were explored surgically. The technical difficulties of utilizing an artificial heart and lung with a persistent left superior vena cava require a precise diagnosis.—*Murray M. Friedman, M.D.*

Varadarajan, M. G. Aneurysm of thoracic aorta with compression of spinal cord. *Licentiate*, July, 1959, *9*, 107–115. (From: Barnard Institute of Radiology, Government General Hospital, Madras, India.)

The author reports the case of a sixty-seven year old male wherein a large syphilitic aneurysm of the descending thoracic aorta eroded the vertebral body of the fourth thoracic vertebra leading to a transverse myelitis and paraplegia.—*Martin A. Thomas, M.D.*

Senn, A., Stampbach, O., Sondergaard, T., and Goetzsche, H. Aktuelle Probleme. (Timely problems.) *Schweiz. med. Wchnschr.*, Mar. 5, 1960, *90*, 229–237. (From: Chirurgische Klinik und Medizinische Klinik der Universität Bern, Switzerland; und Thoraxchirurgische Abteilung der Universität Aarhus, Denmark.)

Open heart surgery for atrial septal defects has the advantage of adequate visual inspection of the "hole" but it is much more of a strain on the patient than closed (blind) methods. Among the latter is Sondergaard's *circumclusio*, in which a catheter is introduced as a guide for the placement of sutures. (The details of this procedure presumably have been reported elsewhere.)

The *circumclusio* had been employed at the time of this publication on 98 patients (47 in Aarhus, Denmark, and 51 in Bern, Switzerland), but this paper discusses only 13 of these who had unusual defects in the atrial septum such as associated anomalous pulmonary venous drainage, coronary sinus defects, septum secundum defects, a dilated foramen ovale, and extracardial veno-venous left to right shunt. Only 1 patient of the 98 died, and this patient's history is summarized. The cause of death was intercurrent miliary tuberculosis, after the successful completion of surgery. Pertinent findings and

rich illustrations assist in understanding the observations selected for presentation—*E. R. N. Grigg, M.D.*

Dummer, Günther M. Zur kinematographischen Darstellung der selektiven Herz- und Lungenangiographie. (Cinematographic demonstration of selective cardiac and pulmonary angiography.) *Thoraxchirurgie*, Oct., 1959, *7*, 287–292. (Address: Witzlebenstrasse 3, Berlin-Charlottenburg 5, Germany.)

The author discusses a special apparatus which permits the combined or simultaneous study of intracardiac and intrapulmonary pressures, blood-gas analysis, selective cardiac and pulmonary angiography (including the capillary phase and venous return), and electrocardiographic tracings without any significant additional burden to the patient or exposure to the patient and examining team. The Müller U G F apparatus has a radiolucent table top, a roentgen tube under the table coupled with the fluoroscopic screen, lead-rubber flaps to protect the examiners, multiple lead attachments for protection of the patient, and a double optic system for simultaneous viewing by two examiners. The magnifier allows a reduction in exposure from 9 r/min. on the skin to 0.9–1.5 r/min. during the fluoroscopic study.

The Ariflex camera used by the author permits 24 frames/sec. at 55 kv., 8 ma.-$\frac{1}{4}$ sec., with 3 mm. Al combined filter, at 50 cm. distance; this gives an exposure of about 5 mr/film. With most large film changers, the exposure may be as high as 250 mr/film. With Odelca and Rapidix-Dassette (maximum 6 frames/sec.) and 120 kv., 20 mas., 3 mm. Al, 55 cm. distance, the exposure is 3,000 mr/film. The author's equipment contains a provision for photoelectric measurement of the intensity so that changes can be made during the procedure for more uniform results.

By means of these studies, minute pathologic changes in the vessels can be recognized long before significant pressure variations occur. The importance to the chest surgeon cannot be stressed strongly enough. The existence of a "second stenosis" within the lesser circulation is of great significance in the preoperative decision with regard to commissurotomy in cases of mitral stenosis. The Müller U G F can be similarly used in bronchography, salpingography, and retrograde pyelography combined with cinematography.—*J. Zausner, M.D.*

Stauffer, Herbert M., Soloff, Louis A., Zatuchni, Jacob, and Carter, Barbara L. Gas and opaque contrast in roentgenographic diagnosis of pericardial disease. *J.A.M.A.*, Mar. 12, 1960, *172*, 1122–1126. (Address: H. M. Stauffer, 3401 N. Broad St., Philadelphia, Pa.)

The differential diagnosis between pericardial disease and other heart conditions has been facilitated by angiography. Intravenous carbon dioxide injection can be safely and conveniently used for roentgenographic demonstration of free pericardial effusion or pericardial thickening localized over the right atrium.

When the carbon dioxide technique is used for pericardial study, the patient is placed with the left side down and the roentgen beam is horizontal. When the right atrium contains gas, its lateral wall appears in the frontal projection as a smoothly curved band with a lateral convexity which is not more than 3–4 mm. in thickness under normal circumstances. When pericardial effusion is present, a soft tissue shadow appears between that of the right atrial wall and the lung so that a widened band of soft tissue density intervenes between the gas and the atrium and the lung. It has been previously pointed out that this position is the one indicated for the treatment of air embolism. As a further precaution to eliminate any possibility of hazard from a residual bubble the authors advocate that the patient remain on his left side for five to ten minutes after the last carbon dioxide injection.

For gas angiocardiography, 100 per cent carbon dioxide is used. One should be certain that the tank contains pure carbon dioxide and not the usual mixture of carbon dioxide and oxygen available in a hospital. The patient is placed in the left lateral decubitus positon, and a No. 19 or 20 guage needle is inserted into the median antecubital vein. The needle is connected to an intravenous drip via three-way stop cocks so that the needle can be kept open in the intervals between gas injections. A 100 cc. syringe with another three-way stop cock is thoroughly flushed several times with pure carbon dioxide and then 100 cc. of the gas is rapidly injected into the vein. An exposure is made at the end of the injection followed by a second exposure within a few seconds. The angiograms are checked immediately after processing and a second injection can safely be made if indicated.

This technique was used 51 times in 40 patients. There was positive evidence of disease in 21, normal findings in 18, and equivocal results in 12 cases. In none of the patients were there any untoward reactions. This technique is of particular value in very sick patients or in those needing only a cursory study of the pericardium. Opaque angiocardiography should be done when a more complete study is indicated, particularly for evaluating underlying heart disease.—*Martin A. Thomas, M.D.*

Santy, P., Papillon, J., Marion, P., Bret, J., Pinet, F., and Chassard, J. L. Étude radiologique de la sténose de l'isthme de l'aorte; à propos de 116 observations; apport de l'angiocardiographie. (Radiologic study of stenosis of the aortic isthmus; report of 116 cases; contribution of angiocardiog-

raphy.) *J. de radiol., d'électrol. et de méd. nucléaire*, Dec., 1959, *40*, 735–742. (From: Centre de Chirurgie cardio-vasculaire, Lyon, France.)

This study is based on 116 operated cases, 67 males and 49 females, varying in age from three months to thirty-six years.

There was a high percentage of asymptomatic patients in whom high blood pressure was fortuitously discovered. In two-thirds of the cases, head symptoms were recorded: headaches, vertigo, tinnitus, and even such complications as meningeal hemorrhage, epistaxis, and hemianopsia. Some cases presented lower extremity complaints, mainly cramps and intermittent claudication. Others showed dyspnea.

In most of the cases a sternal or parasternal systolic murmur was audible, radiating to the back. In 22 cases, a diastolic murmur revealed a coexisting aortic insufficiency. Collateral pulse was positive in 66 cases in the scapular or intercostal areas. One of the cardinal signs of coarctation, *i.e.*, pressure discrepancy in the upper and lower limbs, was found in practically all patients.

Roentgenologic Study. All cases had a standard posteroanterior chest roentgenogram showing the following signs: (1) absence of the aortic knob, noted in 30 per cent of the cases; (2) rib notchings, the most frequent sign, present in 65.5 per cent of the cases and more markedly in 34.5 per cent. Among the 33 cases where rib erosions were not observed, two-thirds of these were patients under fifteen years of age; and (3) cardiac enlargement, present in 63 per cent of the cases. The posteroanterior roentgenogram allows one to judge the size of the ascending aorta which is often dilated. Stenosis was shown in 2 cases and the enlarged left subclavian artery was visible in 8 cases. (This latter sign is to be distinguished from the double aortic knob appearance.)

Aortic Opacification. The purpose of aortic opacification is to study the stenotic segment, the collateral circulation and, eventually, the associated lesions. Among the difficulties inherent to the angiocardiographic technique, the authors mention the dilution of the opaque bolus in the dilated arterial trunks originating from the aortic arch, stasis of the opaque material when aortic insufficiency is present, and lack of contrast by venous injection. For the choice of incidence, an anteroposterior and a lateral projection will give complete and reliable documentation. The seriography depends on the route of the injection. When an intravenous injection is used, the stenosis is usually visible after five to eight seconds. It is most satisfactory in children and thin adults. The aortic injection always secures a good study when made by retrograde catheterization of the right carotid or radial artery or by retrograde injection of the radial artery with controlled hypotension. This last method appears to the authors to be the most efficient. The catheter can be placed close to the stenosis and the hypotension permits better visualization of the collateral circulation while using a lesser amount of opaque medium.

The role of angiocardiography is to evaluate the stenosis. It permits the study of its form (short or long, large or narrow) and its location in relation to the left subclavian artery. It reveals a possible anterior and medial angulation of the stenotic segment due to the ligamentum arteriosum when present. Additional information is obtained concerning the existence, the importance and the location of collaterals and the nature of associated aortic arch anomalies.

Study of the Stenotic Segment. Analysis of the above mentioned elements has led the authors to consider 3 main categories of isthmic stenosis:

(a) Simple Form. This includes the short stenotic segment type which is distant from the left subclavian artery with a normal aorta above and below the stenosis. In these cases, Crafoord's operation is easily performed. This same type may be seen in the presence of a ligamentum arteriosum. On the lateral roentgenogram projection, the extremities of the stenotic segment are displaced anteriorly, the stenosis appearing eccentric to the aorta. As a therapeutic measure, when resection is not feasible as was the case in 3 of their patients, a section of the ligamentum arteriosum often improves the flow of blood.

(b) Complicated Form. A long stenotic segment, distant from the left subclavian artery, sometimes is complicated by the absence of an aortic segment. The prognosis is based on the length of the segment to be resected, because a graft or aortic prosthesis may be necessary. When there is stenosis with a short remaining aortic stump above or none at all, anastomosis will prove to be very difficult. Other complications may be stenosis with an ectatic aorta above and below, and stenosis in the absence of collateral vessels, in which case clamping may produce ischemic zones.

(c) Associated Anomalies. These are numerous and varied. The entire aortic arch may be malformed; the subclavian artery may arise below the coarctation; the stenosis may lie above the ligamentum arteriosum or the arterial canal. Sometimes the stenosis is large and is seen only by angiocardiographic exploration. The coarctation may be low diaphragmatic or abdominal.

Study of the Collateral Circulation. The collateral vessels were visible in 66.4 per cent of the cases and absent in 11.2 per cent. In 19 cases, the degree of opacification was too poor to permit adequate study. The most frequently opacified vessels were the internal mammary arteries, sometimes alone and sometimes with other vessels (74 out of 77 cases). In 26 cases, internal mammary and periscapular vessels were shown. In 15 cases, intercostal arteries were also opacified along with the above mentioned vessels. In 2 cases, only the intercostal arteries were

injected and they were best seen on late roentgenograms taken nine to thirteen seconds after injection under controlled hypotension.

Importance of Angiocardiography. Preoperatively, this examination is of paramount importance, rarely for positive diagnosis of coarctation but mainly for proper evaluation of the stenosis, its type and associated lesions or anomalies. In 1 case, a functional arterial duct was suspected due to the enlargement of the pulmonary artery and the early impregnation of the aorta. In 3 cases, the presence of a patent arterial duct, proved by surgery, explained the poor quality of the angiocardiographic studies due to escape of the opaque medium. A left superior vena cava was demonstrated in 2 cases. One case of total situs inversus was encountered. An atrial septal defect accompanied by an enlarged left atrium, was probable in 1 case as contrast material was seen in the aorta early during the pulmonary phase. There was also a case of interventricular communication with a complex of malformations; the autopsy revealed an aortic coarctation, Roger's disease, and an infundibular type of pulmonary stenosis. An associated mitral stenosis was suspected in another case of coarctation, since the enlarged left atrium remained opacified longer than usual.

Postoperatively, systematic angiocardiography is in current use in Sweden. The authors have employed it only in cases where surgery has already failed or in cases where complicated procedures, such as graft, prosthesis and atypical operations, are considered.—*Henri-Paul Lévesque, M.D.*

Mouquin, M., Brun, Ph., Chartrain, E., Geschwind, H., Pieron, J.-Y., and Bacquet, G. (Paris, France.) Le cathétérisme cardiaque gauche par la voie percutanée fémorale; résultats dans les cardiopathies congénitales et les affections artérielles systémiques. (Left heart catheterization by the percutaneous femoral route; results in congenital cardiopathies and systemic arterial conditions.) *Presse méd.*, Feb. 24, 1960, *68*, 353–356.

After inserting a catheter through the femoral artery up to the level of the aortic arch or into the cardiac chambers, selective angiocardiography may prove quite valuable. Up to the present, very little can be added to the information of right heart catheterization in regard to atrial septal defect. However, it may be useful in studying the atrial ventricular canal, interventricular septal defect, mitral stenosis and insufficiency, aortic stenosis and insufficiency, the aortic-pulmonic window, aneurysm of the sinus of Valsalva, coarctation of the aorta, and patent ductus arteriosus. The method is also of considerable value in coronary arteriography, which will probably be of more concern in the future when improvements in therapy of coronary arterial conditions are at hand.

The authors have studied 250 cases by this method without unusual incidents. Some rather interesting lesions have been demonstrated, such as communication of a coronary artery with the right atrium and also with the left atrium.

It is worth noting the findings given for the atrial ventricular canal; there is an aspect *en accolade* of the septal border of the left ventricle, accompanied by simultaneous opacification of both atria. *Charles M. Nice, Jr., M.D.*

Lull, George F., Jr., and Winn, Dean F., Jr. Chronic fibrous mediastinitis due to Histoplasma capsulatum (histoplasmal mediastinitis); report of three cases with different presenting symptoms. *Radiology*, Sept., 1959, *73*, 367–373. (Address: G. F. Lull, Jr., Fitzsimons Army Hospital, Denver 30, Colo.)

A new approach to the problem of chronic fibrous mediastinitis, which is of importance as one of the major causes of superior vena caval obstruction, is discussed. Three cases of mediastinitis are presented illustrating this new concept, of interest to radiologists as they are in a position to suggest the correct diagnosis. Each of these cases presented in a different fashion, but in each Histoplasma capsulatum was found in the surgical specimen removed at thoracotomy.

The etiologic factor of chronic fibrous mediastinitis leading to superior vena caval obstruction frequently is syphilis or tuberculosis. Bronchogenic malignancy is another, apparently increasing, cause of this condition. There are, however, many instances where a diagnosis of idiopathic mediastinitis has been made, especially after lymphoma, sarcoid, bronchial adenoma, syphilis, tuberculosis, bronchogenic malignancy and other conditions have been ruled out.

Although the roentgen findings in histoplasmal mediastinitis are not at all specific, the authors believe that if the radiologist is alert to minor changes in the mediastinal shadow, and if he evaluates each case in the light of the clinical history, he should be able to suggest the course of investigation to be followed to establish the etiologic diagnosis. The authors believe also that histoplasmal mediastinitis (a term they suggest) is not uncommon and that efforts to establish this diagnosis will decrease the number of idiopathic and tuberculous diagnoses.—*Donald N. Dysart, M.D.*

Brunton, F. J., and Eban, R. E. Sideropenic webs in men. *Clinical Radiology*, Jan., 1960, *11*, 65–67. (From: Radiological Department, St. Mary's Hospital, London, W.2, England.)

Since attention was first drawn to upper esophageal webs forty years ago, the vast majority of examples that have been described have been in

women. The classic syndrome is associated with iron deficiency anemia. The purpose of this communication is to record 3 cases in men who had been subjected to partial gastrectomy, and a further case, also in a man. All 4 were found to be suffering from iron deficiency anemia.

Waldenstrom and Kjellberg in 1939 emphasized that timed spot roentgenograms, using a large bolus of thick barium, were essential to demonstrate the webs. The authors have found that the anteroposterior roentgenogram may be as valuable as the lateral, if not more so, and that it gives equally characteristic appearances. It is clear from a review of the literature that cases of upper esophageal webs may occur in the absence of overt iron deficiency anemia. It is also well recognized that even after the anemia has been cured, the web may persist. Iron deficiency is a well known late complication of partial gastrectomy. Apart from a case reported by Juneau *et al.* (1957), the authors have not found any other recorded instance in men of the sequence: partial gastrectomy, iron deficiency anemia, and upper esophageal web.

In view of the known association of sideropenic webs with malignant disease, they should be suspected and sought for in the postgastrectomy or postgastroenterostomy patient with dysphagia.—*Samuel G. Henderson, M.D.*

Zarabini, G. E., and Recciarini, C. Considerazioni cliniche e radiologiche su cinque casi di esofago breve. (Clinical and roentgenologic considerations in five cases of short esophagus.) *Ann. radiol. diag.*, 1960, *32*, 365–378. (From: Istituti di Radiologia e del Radio dell'Università di Bologna, Bologna, Italy.)

From 90 cases of hiatus hernia, the authors have selected 5 cases of short esophagus. Each case required careful study to determine whether the condition was acquired or congenital.

The embryology of the esophagus is reviewed as it forms in the fetus. It descends from the cervical area until, at the beginning of the third month, it reaches the level of the diaphragm, which it penetrates to reach to stomach. The length of the esophagus is determined by its development and downward descent by the sixth or seventh week of fetal life. It is at this stage of development that a congenital short esophagus is formed. A lax esophageal hiatus plus the negative intrathoracic pressure permits displacement of the stomach into the thorax. Scar tissue as well as pathologic conditions may produce distortion and shortening of the esophagus. Thus, the reducibility or irreducibility of a hiatus hernia is not a clear-cut criterion as to whether or not it is congenital in origin.

In 4 of the 5 cases, a congenital short esophagus was found; in the fifth case, mediastinal and periesophageal inflammation were responsible for the irreducible hiatus hernia.

The 4 patients with a congenital short esophagus had symptoms referable to ulceration or inflammation of the stomach or duodenum; 1 was a cardiac patient.

The authors conclude that, whereas in certain cases a diagnosis of a congenital or acquired short esophagus is possible, at times it may be very difficult to reach any conclusion unless detailed and serial roentgenorgaphic studies are undertaken.—*Peter E. Russo, M.D.*

Blanco, Horacio Gutierrez. Hernias del hiato esofagico, variedad paraesofagica; presentación de 11 casos. (Esophageal hiatus hernias, paraesophageal type; presentation of 11 cases.) *Prensa méd. argent.*, Oct. 16, 1959, *46*, 2493–2506. (Address: 21 de Setiembre 2329, Montevideo, Uruguay.)

Eleven cases of paraesophageal hiatus hernia are reported. Nine of these underwent surgery with good clinical results. Eight of the cases were women and 7 were over fifty years of age; however, 1 of the patients was eleven years old. The reasons for operation included strangulation of the herniated portion of the stomach and intestinal obstruction resulting from herniation of a loop of small intestine. Dysphagia because of displacement and compression of the esophagus was seen in 4 cases. Five patients showed evidence of hemorrhage and 4 suffered a severe chronic hypochromic anemia.

Five of the patients were operated by a transthoracic approach, 3 by abdominal and 1 by combined abdominal and thoracic approach.—*Murray M. Friedman, M.D.*

Abdomen

Longin, F., and Schehl, R. Die vergrösserte Zwerchfell-Magendistanz im Röntgenbild—Ursache und Täuschung. (Increased distance between diaphram and stomach in the roentgenogram—real and apparent.) *Fortschr. a. d. Geb. d. Röntgenstrahlen u. d. Nuklearmedizin*, Jan., 1960, *92*, 20–33. (From: Röntgenabteilung der Med. Poliklinik der Universität Würzburg, Würzburg, Germany.)

The distance between the diaphragm and the superior portion of the stomach varies from 4–7 mm. normally to 1–1.5 cm. during deep inspiration and may reach a thickness of 2 cm. in younger and more muscular individuals. To avoid mistakes in diagnosis, it is necessary to understand the anatomy of the diaphragm and to recognize the differences in the anteroposterior and the lateral arching of the diaphragmatic dome, particularly on the left side. Thus it is necessary to take roentgenograms in various

projections, such as anteroposterior and lateral, both with the patient erect and horizontal, for a better evaluation of the relationship between the diaphragm and the stomach. The findings are different depending on whether the patient is prone or supine and whether the position of the tube is above or below the level of the diaphragm. If a neoplasm of the stomach is suspected, a diagnostic pneumoperitoneum may be required for a correct evaluation.

The diaphragm-stomach distance is increased in a variety of situations: (1) interpositon of the splenic flexure of the colon with or without actual ptosis of the stomach; (2) during deep inspiration; (3) ascites; (4) neoplasm of the cardiac portion of the stomach; (5) interposition of spleen or liver; and (6) collection of fatty tissue around the cardia. The most significant of these, neoplasm of the stomach, may be diagnosed correctly in the presence of corroborative findings such as irregularity and displacement of the distal end of the esophagus, alterations and decrease in size of the gastric air bubble, and destruction of the gastric mucosa, particularly when these are associated with a pertinent history. A spastic or functional contraction of the gastric air bubble can be recognized by the changes produced by the introduction of carbonated beverages and by the fact that the size will vary in the same patient during the course of a diagnostic procedure or during interval studies on different days.

In addition to the technical factors already discussed, apparent increases in the distance between the diaphragm and the stomach may be caused by an enlarged heart, especially when the spleen is simultaneously enlarged or is otherwise interposed between the diaphragm and stomach. Careful study with fluoroscopic control should clarify this condition. Another apparent increase in the distance may be due to relaxation of a portion of the dorsal part of the diaphragm with a consequent shift of the spleen into the depression. Studies in the erect and supine positions will lead to a proper evaluation, since the arching of the diaphragm is less in the supine position.—*J. Zausner, M.D.*

Leigh, Ted F. Acute gastric dilatation. *J.A.M.A.*, Mar. 26, 1960, *172*, 1376–1381. (From: The Department of Radiology, Emory University School of Medicine, Atlanta, Georgia.)

The author presents 4 cases of acute gastric dilatation from his own experience and briefly reviews the entity.

The common predisposing factors are abdominal surgery and trauma, chronic illness, diseases of the spine, confinement and vagotomy. Pertinent clinical findings are distention, vomiting and collapse. The degree of distention is variable. The stomach may contain as much as 7.5 l. of fluid or be filled with fluid and gas in varying proportions. Vomitus is small in amount.

The condition is thought to be due to paralysis of the vagus and splanchnic nerves from central nervous system stimulation. The fluid is derived from oral and gastric secretions and from reflux of bile and pancreatic juices. Swallowed air produces the gaseous distention. There may be associated dilatation of a portion of or the entire duodenum due to acute angulation or traction on the mesentery.

Roentgenographically, the stomach is seen as a large soft tissue mass, or is markedly distended with gas. Fluid levels can be seen on upright and decubitus roentgenograms. Barium enema examination may be used to demonstrate the displacement of the bowel. Angulation of the esophagogastric junction may produce obstruction. This can be demonstrated with contrast media. Gastric intubation may be prevented by the angulation.

Treatment is gastric intubation and suction. Surgery is poorly tolerated.

One of the author's cases occurred following cystoscopy and ureteral catheterization, another after the patient was placed in a spica cast and a third after trauma to the abdomen. All recovered after gastric intubation. The fourth case was of the "idiopathic" variety. The patient died. Postmortem examination showed a huge stomach filled with air and fluid. The stomach was greenish-black in color and necrotic. Gastric perforation had produced peritonitis.—*Barry Gerald, M.D.*

Cantwell, Fermot F. Ward barium meal examination in acute gastro-intestinal haemorrhage. *Clinical Radiology*, Jan., 1960, *11*, 60–64. (Address: St. Vincent's Hospital, Dublin, Ireland.)

Hematemesis may be one of the most alarming emergencies met with in everyday practice. An emergency barium meal technique for roentgen examination has been developed over the past three years which can be carried out in the ward. Food is withheld for two hours. The examination is carried out while the patient is in bed. Four to five ounces of barium is given, and the patient is then rolled onto the right side for a few minutes. Using a mobile roentgen-ray apparatus, the first roentgenogram is taken with the patient lying supine on a cassette. Just before the exposure is made, a mouthful of thick barium is swallowed, which serves to outline the esophagus. The second exposure, in an oblique projection, is then made with the patient prone and the left side raised thirty degrees.

Two hundred patients, with ages ranging from twenty to eighty years, have been examined in this series. The presence of blood in the stomach has not interfered with the interpretation of the roentgenograms. The presence of a peristaltic wave in the stomach on one roentgenogram may cause difficulty in interpretation and may mimic an ulcer crater. Posterior wall gastric ulcers and stomal ulcers are best seen

on the supine roentgenogram. Esophageal and duodenal lesions are best demonstrated on the prone oblique roentgenogram.

Two factors are apparent from previous publications: (1) there is little evidence that early examination disturbs the clot and leads to further bleeding; and (2) the presence of clotted blood in the stomach does not invalidate the findings. These two factors have been borne out in the present series. Many patients have been admitted and readmitted to the hospital with gastrointestinal hemorrhage, and repeated examinations have failed to reveal the cause. Some of these patients have in fact, an acute peptic ulcer which is not demonstrable roentgenologically. A possible explanation for the remaining diagnostic failures may be the delay of three or four weeks before the roentgen examination is carried out, a delay during which small ulcers may heal. It is reassuring for the surgeon to know the site of bleeding before he commences operation.

A positive finding was obtained in 57 per cent of the patients investigated in this series, while confirmed negative findings in a further 25 per cent indicated the presence of an acute ulcer. False positive findings, proved by subsequent examination to be erroneous, were found in 12 ptaients. In 24 patients, lesions found later were not demonstrated by this emergency examination.—*Samuel G. Henderson, M.D.*

Machella, Thomas E. Functional disturbances of the gastrointestinal tract. *Radiology*, Sept., 1959, *73*, 379–397. (Address: 36th and Spruce Streets, Philadelphia 4, Pa.)

Patients with symptoms referable to the gastrointestinal tract must have responsible organic disease ruled out. Only then can symptoms be attributed to functional motor disturbances of this system. The radiologist may be of invaluable assistance in this diagnosis by calling attention to and reporting all motor disturbances encountered during his fluoroscopic examinations and study of the films.

The gastrointestinal tract is controlled by the autonomic nervous system which innervates the effector end plates of the various viscera where inhibition or excitation of function occurs. Stimuli such as hostility, anger, hate and resentment excite the parasympathetic nervous system, which is excitatory to the gastrointestinal tract (excepting its sphincters). Stimuli such as anxiety, fear, worry and sadness excite the sympathetic nervous system, which has the reverse influence.

Esophagospasm, gastric hypermotility, duodenal spasm and hypermotility, and spastic disorders of the small and large intestine are functional disturbances which seem to be due predominantly to parasympathetic influences. Drugs, such as anticholinergics and sedatives, may be used to correct this abnormal physiologic state, along with attempts to help the patient solve his emotional problems which bring on these responses. Disturbances which appear to be due to sympathetic hyperactivity or parasympathetic underactivity comprise achalasia of the esophagus, gastric retention in the absence of obstruction, megaduodenum, and hypoactive states of the colon, including "psychogenic" megacolon. Urecholine, a parasympathomctic drug, has been most useful in these situations.

It is pointed out by the author that, due to differences in innervation of the two halves of the colon, the response to stress stimuli may vary from person to person and even in the same person depending on several factors. Some of these factors are: the relative strength and effectiveness of the two effector divisions of the autonomic nervous system in a given person; the nature, intensity, duration and frequency of the emotional stimulus; and the combined action of several stimuli with opposite effects operating simultaneously. Other factors, such as the ability to accept and adjust to a disturbing situation, the capacity, to ventilate one's problems and to settle problems promptly, also help determine what the response to stimuli will be.

The author feels that it is important to remember, in handling these patients, that should severe functional disturbances persist, definite somatic changes may occur. Achalasia may lead to megaesophagus, and diverticulosis with its various complications may develop from prolonged high intraluminal pressures in an irritable colon.—*Donald N. Dysart, M.D.*

Le Gal, Y., Raber, R., Buck, P., and Simler, M. Étude anatomo-radiologique des prolapsus pyloro-duodénaux. (Anatomic-roentgenologic study of pyloroduodenal prolapse.) *J. de radiol., d'électrol. et de méd. nucléaire*, Dec., 1959, *40*, 743–756. (From: Institut d'Anatomie pathologique de la Faculté de Médecine de Strasbourg, Strasbourg, France.)

Publications dealing with the symptomatic and roentgenologic aspects of pyloroduodenal prolapse are numerous, but anatomic studies are rather scarce. Among the reasons for this scarcity, mention should be made of the unsuitability of necropsy material for the study of fine mucosal changes. Handling and fixation of surgical specimens cause the lesion to disappear as the muscularis is stretched.

After anatomic-roentgenologic correlation, the authors were led to divide cases of pyloroantral prolapse into three types:

1. *Pure Mucosal Type.* The sliding pyloric mucosa produces a prolapse which is mobile and reducible. On roentgenograms the lesion appears inconstant, sometimes visible only on one roentgenogram but, when seen, it resembles the other types of prolapses. This is the type which eludes histologic confirmation because of its lability.

2. *Fixed Type* (*mucosal-fibrous or fibromucosal pro-*

lapses). These are chronic forms of the first type. In this group, the protruding lesion is composed of three layers. The duodenal mucosa is joined to the pyloric mucosa by a thin layer of fibrous tissue (mucosal-fibrous type) or a thick connective tissue band (fibromucosal type). The presence of this fibrous tissue explains the fixity of the lesion on the specimen and its roentgenographic appearance. It is usually located in the superior part of the pylorus and extends as a tongue-like projection into the duodenum with its maximal thickness being along the lesser curvature. It is rarely annular. The protruding part may become polypoid by inflammation or irritative hyperplasia. The direct roentgen signs consist of: a constant filling defect at the base of the duodenal bulb (mushroom or parachute appearance); honeycombed filling defects if the protrusion is polypoid; and lack of duodenal deformities in the absence of an ulcer. The indirect roentgen signs are an enlarged pyloric canal, antral gastritis and hyperkinesia.

3. *Complex Type*. This is a protrusion of a muscular axis from the pylorus. Its inner surface is covered by gastric mucosa and its outer surface by duodenal mucosa. This type results from a progressive and retrograde detachment of the duodenal and pyloric muscularis. The proximal part of the duodenal muscularis lies 1.5 cm. behind the free pyloric border and the pyloric muscularis protrudes into the duodenal lumen.

The pathogenesis of these lesions is explained on the basis of edema of the submucosa of an inflammatory origin. Accompanying features are chronic gastritis with infiltration of the muscularis, and partial degeneration of the ganglion cells. Chronic edema might be the underlying cause of the fixed types of prolapse (mucosal-fibrous and fibromucosal), which are transitional forms of the pure mucosal type. The complex prolapse composed of the complete pyloric muscularis has a different pathogenesis; it is a consequence of a weak point at the junction of the pyloric and duodenal muscularis.

In the differential diagnosis, the authors consider hypertrophy of the pylorus of the adult type, which appears as a long and narrow canal often eccentric to the antrum. A normal duodenal bulb might be seen end-on so that it resembles a prolapse. The duodenal folds converging towards the pyloric opening will help in the differentiation from folds of a herniated gastric mucosa.

In their therapeutic considerations, the authors advise gastrectomy for the fixed and the complex muscular type. In the pure mucosal type, since it is a reducible lesion, corrective surgery with fixation of the mucosa above the pylorus is recommended.—*Henri-Paul Lévesque, M.D.*

Lafferty, John O. Duodenal ulcers in children; with notes on their etiology. *Radiology*, Sept., 1959, *73*, 374–378. (Address: 1012 Kings Drive, Charlotte 7, N. C.)

The occurrence of duodenal ulcer in children is more frequent than is reported in the radiologic literature. In the cases that have been reported, and in most of the cases reported in this article, a psychologic problem was apparent in addition to an active duodenal ulcer. Worry and nervous strain were observed in 2 of the children examined by the author. The first child was a four year old boy who stopped eating and started complaining of severe abdominal pain. Roentgenographic examinations revealed a large crater in the duodenal cap. This child had been well until his parents went to Europe, leaving him and his brother with an aunt. The symptoms were relieved by medical treatment and subsided completely after the return of the parents. There has been no recurrence of any symptoms in seven years. Another child first became ill at the age of seven upon entering school. She had no evidence of active ulcer at that time. However, at the age of fifteen, when she entered high school and began to have dates, she again became ill with vomiting and abdominal pain. Psychiatric history revealed frequent reactions to new situations. She had an active ulcer crater of the duodenum. Medical treatment controlled her symptoms, and she became adjusted to her new school situation.

These children affected by stress often complain of generalized abdominal pain, sometimes with vomiting which recurrs regularly at a particular time of day, differing with the individual. Hunger pain and food relief are rare complaints. Occasionally there will be bleeding. These are not the typical symptoms noticed in the adult ulcer patient. However, as the child grows older, the symptoms become more typical of those in the adult. A positive diagnosis in a child is made when a duodenal ulcer is demonstrated roentgenographically. There is no scarring of the cap or clover-leaf deformity, but often a halo is seen around the crater. Results of nonsurgical treatment are uniformly good. Surgical intervention was not necessary in the 15 children in whom the author found an ulcer.—*W. M. McBride, M.D.*

Gutmann, René-A. (Paris.) Les difficultés du diagnostic entre gastrite et cancer. (The difficulties of diagnosis between gastritis and cancer.) *Arch. mal. app. digest.*, Jan.-Feb., 1960, *49*, 5–38.

The author, an internist, gives 14 case histories from his private file, including mainly instances of "pseudoneoplastic gastritis," by which he means a pseudopolypous appearance of the barium filled stomach caused by hypertrophic rugae, sometimes associated with an inflammatory process. In several instances, there were demonstrable ulcers (one 4 cm. in diameter on the greater curvature) or antral "stenosis," but in most cases conservative management alleviated the subjective symptomatology while at the same time there was more or less complete disappearance of the undesirable roentgen findings. In one pa-

tient (wife and mother of physicians), reexamination after only thirteen days of medical treatment resulted in immediate gastrectomy at which time a large, shallow ulcer on the greater curvature (labeled by the pathologist as being the result of gastritis) was removed. The opinion is expressed that, with more patience, this might have gone to complete healing.

There were 3 malignancies among these cases: 1 with extensive inoperable carcinomatous involvement (resembling pseudopolyposis on the roentgenogram); 1 with lympho-reticulosarcoma (and lymph node metastases); and a most disturbing instance of a forty-five year old female surgical supervisor, with a three and one half year history of dyspepsia and persistent roentgen findings of gastritis, in whom surgery (gastrectomy) removed a malignant ulcer (3 cm. in diameter) from the greater curvature, while metastases were also demonstrated.

The author concludes that, in the presence of both dyspeptic symptomatology and suspicious roentgen findings, one should still place the patient on conservative management, and if his symptoms disappear and the roentgen findings return to "quasi-normal" he may be regarded as "cured." His medical treatment of "gastritis" consists of collargol (colloid silver preparation), oxyferroscorbone (iron with vitamin C), and gastric lavages.

In reviewing the cases reported, one may rightly object that, in some of those who were not subjected to surgery, the time of observation was insufficient to rule out malignancy. Besides, transient, occasionally remarkable, clinical improvement may be encountered in the presence of gastric carcinoma. Knowing the poor results of either, or both, surgical and radiation therapy of epidermoid malignancies of the stomach, a certain amount of procrastination would appear to be justified. On the other hand, even extensive involvement should not preclude surgical exploration, since there is always the possibility that the lesion is a quite "curable" leiomyosarcoma.—*E. R. N. Grigg, M.D.*

Amberg, John R. Accuracy of roentgen diagnosis in carcinoma of the stomach. *Am. J. Digest. Dis.*, Mar., 1960, *5*, 259–263. (Address: Milwaukee County Hospital, Department of Radiology, Milwaukee 13, Wis.)

The author reviewed all reports of stomach examinations for the period 1939 through 1950 which were performed at the University of Minnesota Hospitals. These were correlated with the case histories of gastric cancer indexed in the records. About 35,400 examinations were done on 21,700 patients. Eight hundred sixty-one cases of carcinoma of the stomach were found during this period.

The figures were analyzed as to false-positives, false-negatives, and also as to the delayed diagnosis group. In the false-positive group there were found to be 67 false-positives out of 861 cases, or a percentage error of 7.8 per cent. Most of these were disproved by autopsy or operation and of this group over half were demonstrated to be benign gastric ulcers. Other gastric lesions were found and, of these 67 false-positives, only 7 had completely normal stomachs; this indicates that roentgen examination is sensitive in screening the normal from the abnormal but is less accurate in obtaining a specific histologic diagnosis.

In the false-negative group, in which there were 72 cases out of 361 carcinomas with a percentage error of 8.4 per cent, the greatest source of error was in gastric ulcer and lesions causing pyloric obstruction. Only 5 of these examinations were considered completely negative, however, with 46 out of 72 considered as most likely benign lesions and 21 as either a benign lesion or possibly a malignancy. Most of these patients were treated aggressively with very few being re-examined following medical management. The survival figures in this group demonstrate an increased survival rate of 16 per cent in the false-negative group and 7.8 per cent in the whole group. This would tend to indicate that the lesions most difficult to identify positively as malignant are, on the whole, more favorable lesions as far as surgery is concerned.

The delayed diagnosis group is very difficult to evaluate because very little definite information can be obtained. There is the general impression that, in lesions which are difficult to diagnose, the prognosis is apparently better. It may be that some from this group should be included in the false-negative classification and, if so, it would make that figure larger.—*George L. Sackett, Jr., M.D.*

Brown, Charles H. Carcinoma of the pylorus simulating benign duodenal obstruction. *Am. J. Digest. Dis.*, Mar., 1960, *5*, 264–273. (From: Department of Gastroenterology, The Cleveland Clinic Foundation, and The Frank E. Bunts Educational Institute, Cleveland, Ohio.)

Gastric obstruction in a patient with a long history of duodenal ulcer is usually benign. Carcinoma of the stomach is relatively uncommon in these patients. However, the author reports 3 cases which point out that complete reliance cannot be placed on these facts.

The first case had prompt relief of obstruction by medical management and the patient refused follow-up studies until the obstruction recurred four and one-half months after the initial obstruction. At that time a far-advanced obstructing pyloric carcinoma was found.

The second case had a five year history suggestive of ulcer. Roentgenographic examination showed a greatly dilated stomach. The pylorus and duodenal bulb were not well shown. There was no improvement after eleven days of medical therapy. Operation was performed and a localized pyloric carcinoma was found.

The third case had a long history of ulcer symptoms and became obstructed. This patient was considerably relieved by medical therapy, but progress roentgen studies suggested an annular lesion of the pylorus, which was removed surgically and found to be a carcinoma.

In a patient who is obstructed, complete reliance cannot be placed on a history of duodenal ulcer and relief of obstruction following medical therapy does not exclude the possibility of pyloric carcinoma. Persistent obstruction despite intensive medical treatment strongly suggests pyloric carcinoma and makes operation advisable.

The author urges that delay be avoided in these cases of pyloric obstruction and believes that in most cases the patient will be sufficiently relieved after fourteen days of intensive medical therapy, so that an accurate diagnosis can be made by roentgen studies.—*George L. Sackett, Jr., M.D.*

Daniels, Virgil C., and Wood, Ernest H. Diverticulitis of cecum and ascending colon. *J.A.M.A.*, Feb. 6, 1960, *172*, 519–524. (Address: V. C. Daniels, 501 11th St. N., Chapel Hill, N. C.)

In 5,000 colon examinations, diverticula of the cecum and ascending colon were found in 10 patients. Five of these 10 also had diverticulitis and these 5 cases are reported. The authors believe that an increased awareness of the disease would result in a more frequent preoperative diagnosis.

The diverticula are either of the true (congenital) or acquired type. True solitary diverticula occur most commonly within a segment 2 cm. above or below the ileocecal junction. The false or acquired type is generally multiple and occurs throughout the colon from the ileocecal valve to the rectum. Patients with acute cecal diverticulitis commonly present a clinical picture of acute abdominal disease localizing in the right lower quadrant, and a diagnosis of appendicitis or appendiceal abscess is made. Only 6 per cent of these patients are correctly diagnosed preoperatively.

A history of previous attacks which subsided spontaneously and the finding of a palpable mass in the right lower quadrant should suggest this disease. Roentgenographic barium enema examination should be done to establish the definite diagnosis; a plain survey roentgenogram usually is of no value. Although the diverticula often contain enteroliths, these are infrequently calcified. The barium enema may outline the diverticula or, more characteristically, demonstrate a localized, discrete, eccentric intramural indentation of the barium column. The overlying mucosa is intact, but edematous and transverse folds are often crowded together. The involved bowel is often fixed, and a large area adjacent to it exhibits inflexibility and limited distensibility. As with diverticulitis of other areas of the colon, the junction of the involved area with adjacent normal colon is gradual and smooth. One must be judicious in application of barium enema examination for the patient with an acute abdomen inasmuch as it is ordinarily contraindicated in the presence of acute appendicitis.

The solitary type of diverticulum usually does not fill with barium, and diagnosis depends upon recognition of secondary changes. A diverticulum containing an enterolith may present a ring shadow appearance. The appendix, when present, usually fills with barium, which is rare with appendiceal disease.

Three of the 5 patients were operated. The remaining 2 were treated conservatively with good results. *Richard F. Fox, M.D.*

Skokan, Z. V. Acute pneumocholecystitis. *Radiol. clin.*, Jan., 1960, *29*, 22–27. (Address: Roentgen Department, Hygienic Faculty of Charles' University, Praha 12, Czechoslovakia.)

Thirty-nine cases of acute pneumocholecystitis diagnosed by roentgenographic examination have been reported in the literature, and 1 additional case is added.

Age incidence varied from twenty-seven to seventy-five years, with the majority between fifty and seventy years. Males outnumbered females 3 to 1. The most frequent causative organisms were *Clostridium welchii* and *Escherichia coli*.

The onset of the symptoms was abrupt, and the clinical picture indistinguishable from acute cholecystitis without gas formation. The temperature was subfebrile; the white blood cell count was elevated.

Roentgenographically, lithiasis was found in few cases but stones were discovered in all operated cases. Diabetes was present in about a third of all cases reported. The diagnosis is made from plain roentgenograms which demonstrate gas in the lumen of the gallbladder and sometimes in the biliary tree. This must be differentiated from gas which has entered through a fistulous communication with the gastrointestinal tract or through an incompetent sphincter of Oddi. The gallbladder may be distended with gas and, if therapy is not started, the distention may increase in degree. In untreated cases the gas may penetrate the wall and form a concentric ring of lesser density around the fundus or entire gallbladder.

In the case reported, the plain roentgenogram showed a gallbladder slightly distended with gas, and with no fluid level shown on the erect roentgenogram. After the acute symptoms had passed, roentgenographic examination of the stomach showed no passage of opaque material into the biliary system. A fortnight later, when the gallbladder distention had diminished, the hepatic ducts and ductus choledochus were visualized with biligrafin and the opaque material passed into the duodenum, but the gallbladder did not fill.

The author's criteria for diagnosis of acute pneu-

mocholecystitis are as follows: (1) presence of gas in the lumen of the gallbladder and gas infiltration of the wall; (2) typical clinical symptoms of acute cholecystitis; and (3) exclusion of pathologic communication of the gallbladder and biliary tree with the digestive tract.—*Lois Cowan Collins, M.D.*

Frommhold, W., and Braband, H. Zwischenfälle bei Gallenblasenuntersuchungen mit Biligrafin und ihre Behandlung. (Types and treatment of complications following the use of biligrafin in studies of the gallbladder.) *Fortschr. a. d. Geb. d. Röntgenstrahlen u. d. Nuklearmedizin*, Jan., 1960, *92*, 47–59. (Address: W. Frommhold, Canovastr. 9, Berlin-Friedenau, Germany.)

The role of biligrafin in the 22 known deaths among 6.2 million examinations throughout the world since 1953 is discussed. The cause of death is frequently not clear, but respiratory disturbances such as pulmonary edema suggest an allergic reaction; and vascular collapse suggests a pre-existing serious disease of the cardiovascular system or a powerful vago-vagal reflex triggered by the hypertonicity of the contrast material. Even though the mortality rate is exceedingly low, certain precautions are essential: (1) a real and urgent indication for the use of this medium must be present; (2) the patient must be asked about any past allergic reactions; (3) only a physician may give the injection; (4) the patient should be lying down (never in a sitting position) for the injection; and (5) the patient must be observed for a suitable period of time after the injection.

All injections should be made in a room especially set aside for the purpose and equipped to handle the complications. Allergic skin reactions such as localized reddening at the site of injection, urticaria, or edema of the eyelids may be treated according to their severity by intravenous injection of calcium, antihistamines or cortisone. Mild generalized reactions such as nausea, vomiting, a feeling of warmth, sneezing, a tickling sensation, or cough indicate the need for fresh air or oxygen administration, calming of the patient, and careful supervision by the physician for a suitable period of time. For the more serious reactions, oxygen therapy is most valuable. Respiratory symptoms such as tachypnea, dyspnea, asthmatic attack, or glottis edema may be relieved by the intravenous injection of cortisone (25–100 mg.), antihistamines (20–50 mg.), or calcium (10 cc.). Cardiovascular signs such as angina pectoris or a feeling of impending death should be treated with vasodilators or barbiturates, whereas paleness, profuse perspiration, and circulatory collapse may require infusions of physiologic NaCl with 5 per cent glucose (with noradrenalin, 4 mg./500 cc.) and cortisone (25–100 mg.). Convulsions or tonic-clonic cramps may require barbiturates intravenously administered or, in more serious cases, general anesthesia.—*J. Zausner, M.D.*

Glenn, Frank, and Redo, S. Frank. Mitral stenosis and biliary tract disease. *Ann. Surg.*, Jan., 1960, *151*, 139–145. (From: Department of Surgery, The New York Hospital—Cornell Medical Center, New York.)

The authors present a brief review of a previously published paper of 1958 dealing with 300 cases and add an additional 100 cases. All 400 patients had both evidence of gallbladder disease and surgery for mitral valvular disease. A comparison by decade age groups and sex revealed a significant increased incidence of gallbladder disease in patients operated on for mitral valvular disease for white males under sixty-one and for white females under fifty-one. The routine at the authors' hospital now is cholecystography as a preoperative examination in all patients with mitral disease. If gallbladder disease is present and if the heart surgery is not of emergent necessity, the gallbladder is resected first, followed by an adequate rest period before the heart surgery is done. Such a plan is supported by the eventuality of trouble in patients with gallbladder disease, increased incidence of acute cholecystitis in postoperative patients, and difficulty in differentiating acute right heart failure from acute cholecystitis in the postoperative patients.

The authors present the theory that the reason that gallbladder disease and mitral valvular disease are associated is because of repeated transient episodes of right heart failure with related hepatic congestion.—*L. Ray Stewart, M.D.*

Palacio, E. J., Alzugaray, A. E., Bolo, P. O., Hojman, D., and Zelasco, J. F. Sindrome de Dubin y Johnson y miastenia gravis. (Syndrome of Dubin and Johnson and myasthenia gravis.) *Prensa méd. argent.*, July 31, 1959, *46*, 1943–1947. (Address: E. J. Palacio, Bolívar 890, Buenos Aires, Argentina.)

The syndrome of Dubin and Johnson is an uncommon disease with a familial tendency, characterized by chronic cholemia and mottling of the liver. The jaundice is variable. About one-half of the patients show a palpable liver and dark urine. Twelve per cent have diminished biliary secretion. The liver has the capacity to conjugate bilirubin with glucuronic acid, but is not able to excrete it in the bile. For this reason, the bilirubin-glucuronic acid is regurgitated in some form into the blood and lymphatic system. In the blood, it is probably reconverted to bilirubin. Biopsy specimens show a characteristic deposition of pigment in the region of the central lobules and rarely in the Kupffer cells. This condition is compatible with a normal life and the prognosis is excellent.

A case of Dubin and Johnson's snydrome is presented. However, this patient also suffered from myasthenia gravis which eventually caused his death.

The syndrome must be differentiated from other conditions such as Gilbert's disease, posthepatitis, biliary hypertension and cholangiolitis. In the cases of intermittent jaundice with negative cholecystograms, no evidence of biliary hypertension, a normal prothrombin time, and an enlarged liver, a biopsy is indicated for diagnosis.—*Murray M. Friedman, M.D.*

Genitourinary System

Winter, Chester C. The excretory urogram as a kidney function test. *J. Urol.*, Mar., 1960, *83*, 313–318. (From: Department of Surgery, Division of Urology, University of California Medical Center, Los Angeles, Calif.)

The author uses clinical observations, the degree of density of the opaque medium in the kidneys on intravenous urography and various clearance studies to evaluate the excretory urogram as a test of kidney function. He points out that hypaque is excreted by the renal tubules at low levels of plasma iodine concentration, and at high levels by the glomeruli. Because of the high iodine concentration produced by intravenously administered hypaque, the density of the opaque medium seen on the pyelograms may be normal, even though there is definite renal damage. Furthermore, the author has shown that lesions of the renal artery, which might result in diminished blood supply to the kidney, do not produce significant changes on the intravenous pyelogram.

Of 72 patients studied in this series, 32 per cent had good pyelograms in spite of significantly diminished kidney function.—*George W. Chamberlin, M.D.*

Hamm, Frank C., Waterhouse, Keith, and Weinberg, Sidney R. Dangers of excretory urography. *J.A.M.A.*, Feb. 6, 1960, *172*, 542–546. (Address: F. C. Hamm, 121 DeKalb Ave., Brooklyn, N. Y.)

The diagnostic value of excretory urography justifies its extensive use, provided its limitations are recognized and its dangers are appreciated. It is undoubtedly the best method for routine screening of the urinary tract before prostatic surgery and for postoperative check after pyeloplasty, ureteral anastomosis, or a urinary diversion. It is also the preferred method of appraisal of the kidneys in patients with malignancy arising in the pelvis.

The authors point out that there are some dangers in excretory urography, but, if care is exercised, they may be minimized. In a series of 21,525 excretory urographic examinations there were 4 serious reactions but no fatalities. These were in 2 men aged thirty-five and sixty-nine and 2 women aged forty-four and sixty-one. Three of these serious reactions occurred after the injection of 50 per cent hypaque, and 1 after the injection of 50 per cent neo-iopax. Two of the 4 reactions occurred immediately, a third within ten minutes after the injection of contrast material, and the fourth was more delayed, occurring thirty minutes after the injection. The symptoms consisted of labored breathing, cyanosis, rapid pulse and, usually, shock.

Treatment of these patients should fall into three phases: (1) establishment of an adequate airway with oxygen and artificial respiration if required; (2) support of blood pressure with intravenous infusion of 5 per cent glucose and vasopressors if necessary; and (3) intravenous injection of an antihistamine.

Every precaution must be taken to prevent reactions after administration of an opaque medium. Severe allergies and asthma are contraindications to excretory urography. Use of antihistamines routinely prior to injection of contrast material is advocated. Some mild sedation is helpful to relieve apprehension and air swallowing. Since the reaction may be delayed, the authors use a test dose of 1 cc. given intravenously and observe the patient for thirty minutes before injecting the remainder of the material.—*Robert J. Yingling, M.D.*

Lowman, Robert M., and De Luca, James T. Nephrotomography: its role in routine urographic studies. *J. Urol.*, Mar., 1960, *83*, 308–312. (From: Department of Radiology, Yale University School of Medicine, Yale Medical Center, New Haven, Conn.)

This report describes the use of nephrotomography with routine intravenous pyelographic studies. The authors' technique includes a survey roentgenogram and a survey tomogram prior to the injection of 50 cc. of hypaque. Subsequently, in the average patient tomograms are made at 7, 8 and 9 cm. levels as measured from the table top. The use of the multifilm cassette is recommended for this purpose. After the completion of the nephrotomograms, the routine urograms are then made at five, fifteen and thirty minute intervals.

The advantages of nephrotomography are the elimination of overlying bowel shadows and better demonstration of the renal, parenchymal and excretory system with differentiation of mass lesions of the kidney and perinephric tissues. This results in a decrease in the number of additional studies and elimination of unnecessary instrumentation for the patient.

Eight roentgenograms and tomograms illustrate the value of the procedure in various pathologic states.—*George W. Chamberlin, M.D.*

Roth, H. W., Movarrekhi, H., and Wenger, P. Le néphrogramme isotopique; méthode, analyse quantitative et utilité clinique. (The isotopic nephrogram; method, quantitative analysis and clinical application.) *Schweiz. med. Wchnschr.*, Mar. 12, 1960, 286–292. (From: Clinique universitaire de Médecine

interne and Institut du Radium, Genève, Switzerland.)

Isotopic nephrography is a relatively new method of evaluating renal function. A scintillation counter is placed over both kidneys and the bladder successively, following an intravenous injection of 2 μc of I^{131}-tagged diodrast per 10 kg. of body weight. The curves are recorded directly and results may be obtained within approximately twenty minutes after the injection.

This method is of considerable value when there is interest in the separate function of the kidneys. The evaluation of the function of the respective kidneys is much more accurate than with intravenous pyelography. The method takes much less time and involves less discomfort for the patient than ureteral catheterization studies.

The procedure is useful in the study of urinary tract occlusions, pyonephritis, hypertensive disease and any condition where appraisal of unilateral kidney function is important or where there is intermittent kidney dysfunction.—*Charles M. Nice, Jr., M.D.*

McGovern, John H., Marshall, Victor F., and Paquin, Albert J., Jr. Vesicoureteral regurgitation in children. *J. Urol.*, Feb., 1960, *83*, 122–149. (From: Department of Surgery [Urology], Cornell University Medical College, and Department of Surgery [Urology], James Buchanan Brady Foundation, of the New York Hospital, New York 21, N. Y.)

Reflux of urine from the bladder into the ureters can be demonstrated roentgenologically. Such reflux is a useful sign of urinary tract abnormality and is an important part of a diagnostic study, particularly in children. The authors demonstrate that vesicoureteral regurgitation has been found only rarely, if at all, in normal children. It is a frequent finding in children with urologic signs and symptoms, and when it is present it indicates the probability of other urinary abnormalities.

The technique is relatively simple. A catheter is inserted into the bladder and a nonirritating radiopaque fluid is allowed to gradually distend the bladder over a period of two or three minutes. The radiopaque material runs into the bladder under gravity pressure of approximately 15 cm. of water. By such a method, one can obtain a useful measure of the bladder volume and configuration. Urograms are made in the anteroposterior and oblique positions after the catheter has been removed. It is then desirable to try to obtain voiding urograms in the anteroposterior or oblique positions and, if reflux is demonstrated, another urogram taken ten minutes later may provide information regarding the adequacy of emptying of the upper urinary tract.

When dealing with children, general anesthesia is frequently required. Under such circumstances, the technique is the same. If the anesthetized patient does not void spontaneously, pressure can be brought to bear on the bladder until the urinary stream is started.

This article is an excellent review of the literature and the authors' experience with vesicoureteral regurgitation. It includes numerous case reports and summary of experience with 43 children who were treated surgically. The structure of the ureterovesical junction is discussed as it concerns regurgitation along with the proper surgical procedures for reinsertion of the ureter into the bladder to prevent such regurgitation. The authors note various degrees of severity, some mild and some marked.

In general, the prognosis of those patients who demonstrate evidence of vesicoureteral regurgitation is unfavorable. All upper urinary tracts which show evidence of reflux are supposedly dying, but at different rates. Although nonsurgical management may sometimes produce improvement, fundamental and permanent restoration can only be achieved by surgery.

Proper diagnosis includes the recognition of those circumstances in which damage is already so great that there is no reasonable prospect of restoring adequate function. In such cases, prompt maximal drainage is usually the treatment of choice. Proper selection and adequate treatment of many of these patients with urinary tract disease has resulted in a normally functioning excretory system.—*George W. Chamberlin, M.D.*

Iannaccone, A., Gabrilove, J. L., Brahms, S. A. and Soffer, I. J. The roentgen diagnosis of adrenal tumor in Cushing's syndrome. *A.M.A. Arch. Int. Med.*, Feb., 1960, *105*, 257–263. (Address: J. L. Gabrilove, 79 E. 79th St., New York, N. Y.)

Intravenous urography, with perirenal air insufflation and oblique roentgenograms, is the most important method for establishing the presence or absence of adrenal tumors in Cushing's syndrome.

If a mass is seen on the plain roentgenogram, it is in all probability a carcinoma.

Benign tumors are much smaller than carcinomas and are more difficult to detect roentgenographically. Gas insufflation is essential for their demonstration. Particular attention must be paid to localized, rounded or protuberant densities of the adrenal gland or irregularity in its contour. The authors do not make a diagnosis of adrenocortical atrophy roentgenographically.

In the absence of a tumor, normal-sized or bilaterally enlarged adrenal glands are noted in Cushing's syndrome.—*James J. McCort, M.D.*